Strategies to Reduce Hemodialysis Catheter-Related Complications

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VRIJE UNIVERSITEIT

STRATEGIES TO REDUCE HEMODIALYSIS CATHETER-RELATED COMPLICATIONS

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Progress in medicine is always bothered by its resistance against change
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Voor Bram, Zimme en Jolieke

Contents

1 Introduction

Temporary vascular access for hemodialysis treatment.

Adapted from:

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Since Dr. Wilhelm J. Kolff first introduced the artificial kidney in 1943 and started his first hemodialysis treatment in the Stadsziekenhuis in Kampen [1], it was clear that proper access to the circulation for repetitive dialysis treatment would be the Achilles' heel of chronic dialysis treatment. His first patient died after 34 days of dialysis treatment because possibilities for access were exhausted. From this early observation on, it has become clear that whatever access device was chosen to obtain access to the bloodstream, it should have a number of qualities. The access should be easily available for connection to the dialysis machine at least three times a week and should provide adequate blood flow of 200-500 ml/min. After treatment, disconnecting should be possible relatively rapid. In addition, complication rates like bleeding, thrombosis and infection should be low and discomfort for the patient minimal. An arteriovenous fistula on the forearm as developed first by Brescia and Cimino in 1966 [2], embodies most of these features and is still considered the best option for access to the bloodstream for patients on chronic hemodialysis treatment. After a period of maturation of about 6 weeks, repetitive access to the circulation can be obtained by puncturing the dilated veins. Unfortunately, an arteriovenous fistula is not always possible because of insufficient diameter or maturation of the veins. The most common alternative is the placement of a subcutaneous arteriovenous graft. These have the advantage that maturation is not needed and are available for puncturing after 2 to 4 weeks. Arteriovenous grafts have a substantially higher risk for thrombosis and infection than arteriovenous fistula and are considered second best [3].

However, a significant number of patients present with acute renal failure or have no adequate arteriovenous access available when they reach end stage renal failure and require hemodialysis treatment. Mostly, this is because of slow maturation of their fistula. Likewise, patients with failure of previously available renal replacement therapy such as transplantation or peritoneal dialysis often do not have a functional arteriovenous access. All these patients require a temporary vascular access by means of a hemodialysis catheter to achieve immediate access to the circulation for adequate dialysis treatment. Hemodialysis catheters are available as untunneled catheters (UCs), used when a catheter is needed for only a short period of time, and as tunneled cuffed catheters (TCCs) when a catheter is needed for longer periods. UCs are relatively small bore (11–13 Fr) catheters and have no cuff adhered to the catheter. These can be inserted with relative ease by a bed-side procedure under local anesthesia without the formation of a subcutaneous tunnel and are usually intended to be used for up to 2-3 weeks. In current practice the use of temporary hemodialysis catheters is substantial. From the recent data of the Dialysis Outcomes and Practice Patterns Study (DOPPS), it is recognized that 15-50% of patients in Europe and 60% of patients in the US start hemodialysis treatment with a catheter for vascular access [4]. However, such widespread application of catheters exposes patients to an enhanced risk of catheter-related complications. Because of these complications, about 50% of all temporary catheters have to be replaced which results in substantial patient morbidity as well as additional consumption of resources, nursing and nephrologists time [5;6]. Tokars et al. [7] demonstrated in a prospective study including hemodialysis patients with a catheter that they had a relative risk for infection of 2.07 compared to patients with an arteriovenous fistula

or graft. A third of these patients had to be hospitalized because of the infection. In order to prevent the most important catheter-related complications, i.e. infection and thrombosis, and to optimize the survival of a catheter, a number of considerations have to be taken into account. The duration for which a catheter will be needed is the most important. Considerations include decisions on the optimal site and method of cannulation, the type of catheter used and whether the catheter should be tunneled or not. In addition, the access team must determine what kind of dressing should be used and whether antimicrobial ointment and/or antimicrobial locking solutions should be applied. A thorough protocol for connecting and disconnecting blood lines must be available, as well as a protocol on how to treat catheter-related complications. Whether post procedural checks like chest X-rays, often postponing dialysis treatment, are really needed is questionable.

Recently the National Kidney Foundation - Dialysis Outcome Quality Initiatives (NKF-DOQI) Clinical Practice Guidelines for Vascular Access have been updated and published [3]. These guidelines can be of use when making decisions on hemodialysis catheter-related procedures and on care-giving protocols. However, new strategies have emerged that may prevent catheter-related bacteremia and dysfunction and reduce patient morbidity and mortality.

DETERMINATION OF THE TIME DURING WHICH A CATHETER IS NEEDED

There are numerous clinical situations in dialysis for which acute vascular access is required. The specific clinical situation of the patient usually determines for how long a hemodialysis catheter is needed and what the chances for renal recovery are. These two factors determine at large the decisions on the cannulation site and on the type of catheter that is needed.

Acute renal failure and exchange therapy

In acute renal failure requiring immediate dialysis treatment and in case of plasma exchange therapy, vascular access by means of a temporary catheter is the best choice. Usually, a femoral catheter will be inserted because treatment can be started without delay, which can be essential for example in cases of life-threatening hyperkalemia. The cause of renal failure can be analyzed and an approximation can be made of the time period during which dialysis is needed. However, femoral catheters should not be left in place for more than 1 week because they are associated with an increased risk of infection and dysfunction [8]. When recovery of the renal function is unlikely and the need for chronic dialysis treatment is expected, the use of the subclavian vein for inserting a catheter should be prevented because of the high risk of central vein thrombosis [9;10]. This can compromise arteriovenous access in the future.
NKF- DOQI guidelines recommend that when can be foreseen that a catheter is needed for more than 3 weeks, a tunneled cuffed catheter should be used. However, it has been recognized that this recommendation is largely opinion based.
In continuous renal replacement therapy in the intensive care unit (ICU) femoral catheters are frequently used. Although there are no data on double-lumen dialysis catheters in the ICU patient, it has been shown that femoral catheters that are used for infusion have an increased risk of infection [11]. Therefore, subclavian or jugular catheters should probably be preferred in ICU patients.

Chronic renal failure and failure of peritoneal dialysis treatment

Despite the fact that increasing attention is paid to the timely creation of a functional arteriovenous fistula or graft in the predialysis care, most commonly, a catheter is inserted because hemodialysis treatment is needed for end-stage renal failure resulting from known progressive chronic renal failure [4]. In most of these patients creation and maturation of a functional arteriovenous access will take at least several weeks.
It is preferable to start with a jugular catheter that can provide adequate dialysis for this period. Whether this should be a tunneled catheter will be discussed in the paragraph on tunneled versus untunneled catheters.
The same accounts for failure of peritoneal dialysis. Removal of a peritoneal dialysis catheter can be necessary for persistent or relapsing peritonitis. Another common cause for interruption of peritoneal dialysis treatment is the failure of ultrafiltration.
In both cases vascular access catheters often have to remain in place for months.
In a substantial number of these patients, infection or ultrafiltration failure results in a definitive transition to hemodialysis.

CANNULATION SITES

Once the duration for which a hemodialysis catheter is needed has been estimated, the next decision that needs to be made is which cannulation site is best. Generally, the femoral, subclavian or internal jugular veins are used. In patients with exhausted access due to thrombosed veins or infection, exotic routes like translumbar or transhepatic routes may be necessary [12;13]. Even long-term arterial cannulation has been used for dialysis [14]. Because these routes are rarely necessary, they will not be discussed in detail.

Femoral vein

The femoral vein is preferred when rapid access is needed because of the underlying condition of the patient or for logistic reasons. Insertion is relatively easy, complications are rare and treatment can be started without delay. In addition, it is the preferred site when patients can not lie flat because of dyspnea and in case of severe coagulation disturbances. With modern flexible catheters, patients can even be mobilized [15].
According to the NKF-DOQI guidelines, there are data that recommend that untunneled femoral catheters should not be left in place for more than 5-7 days because of the high risk of infections. Oliver et al. [8] demonstrated in a study in 218 patients that the subset of patients with femoral catheters had a high incidence of bacteremia (10.7%) when the catheter was left in place for more than 1 week.
However, occlusive dressings were applied in this study and there was no strict protocol for the removal of catheters in case of exit site infection.

Subclavian vein

The NKF-DOQI guidelines recommend that the subclavian vein should not be used in patients who need permanent vascular access because of a high risk of subclavian vein thrombosis. Schillinger et al. [10] compared in a prospective study the outcome of 50 subclavian with that of 50 jugular hemodialysis catheters and found an incidence of 42% subclavian stenosis compared to 10% jugular stenosis. Subclavian stenosis and occlusion can lead to arm edema and can hamper the development of an adequate arteriovenous fistula or graft in the future. This indicates that in all patients with chronic renal failure, vascular access through the subclavian vein should be avoided.
Another disadvantage of subclavian vein cannulation is that it requires more skills of the operator and is associated with more severe insertion complications such as pneumothorax and hemothorax. Notwithstanding these guidelines it was shown in the DOPPS that in the US 46% of all temporary catheters used in patients starting hemodialysis treatment were inserted into the subclavian vein. Probably, the reason for this widespread use of subclavian catheters is the observation that they have a lower risk for infectious complications than untunneled jugular catheters [6].
Subclavian catheters are more comfortable for the patient and provide reliable blood flow if placed in the right atrial cavity.
Therefore, the subclavian site should only be used if a catheter is needed in patients with acute renal failure when renal replacement therapy is expected to be temporary or when the jugular site is not available.

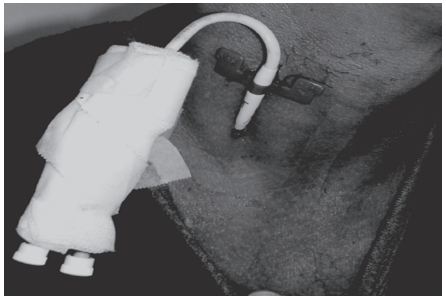

Figure 1.
Uncomfortable position and poor fixation of a straight jugular catheter.

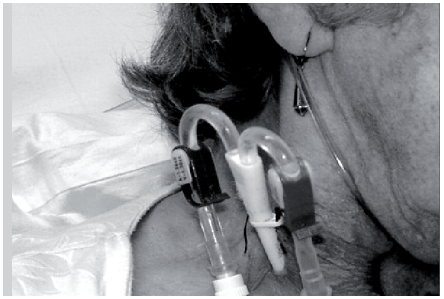

Figure 2.
Uncomfortable position and poor fixation of an untunneled jugular catheter with curved extensions.

Internal jugular vein

A hemodialysis catheter in the internal jugular vein is preferred for patients on chronic dialysis treatment. Cannulation is easy, especially when inserted with the use of ultrasound localization of the vein and the complication rates are low [16]. The right jugular site is preferred because of the straight intravascular route to the right atrial cavity. Left situated jugular catheters can also be used but are associated with more complications and shorter survival compared to right jugular catheters [17;18]. The most important problem of jugular catheters is that they are uncomfortable for the patient because neck and head movements are limited. This holds especially true for straight, high-inserted, precurved catheters (fig. 1) and jugular catheters with a curved extension (fig. 2).

These catheters have a higher rate of infectious complications compared to subclavian catheters [6]. Probably, this is because adequate fixation is hampered by continuous movements of these catheters with movements of the head and by downward pulling of dialysis tubes at the extensions when connected to the hemodialysis machine. In addition, these catheters have an upward directed exit site which in analogy to peritoneal dialysis catheters might be associated with an increased risk for exit site infections as has been demonstrated for peritoneal dialysis catheters [19;20].

SHOULD A CATHETER BE TUNNELED?

Using the limited data available on complication rates of straight untunneled jugular catheters with curved extensions, the NKF-DOQI guidelines recommend that a tunneled cuffed catheter should be inserted when it can be anticipated that a catheter will be needed for more than 3 weeks [3]. Even when a catheter is needed for less than 3 weeks, inserting a tunneled cuffed catheter is acceptable. However, inserting a tunneled cuffed catheter requires prolonged procedure time and special skills of the physician.
In addition, its removal is hampered by growth of subcutaneous tissue into the cuff adhered on these catheters. These drawbacks for the use of tunneled catheters

might explain the observation in the DOPPS that untunneled catheters are still widely used beyond the recommended 3 week period. In incident hemodialysis patients, 48% of catheters in the US and 75% of catheters in Europe are untunneled. Even in prevalent patients over a third of all catheters are untunneled [4].
As was pointed out recently, there are limited data available in the literature comparing the outcome of untunneled and tunneled cuffed catheters [21]. Reported bacteremia rates vary from 3.8-6.5/1,000 catheter-days for untunneled catheters to 1.6-5.5 for tunneled cuffed catheters [5;6;8;22;23]. In these studies, catheter care protocols and the definitions of complications differ. In addition, because untunneled catheters and tunneled cuffed catheters are used for different clinical situations, the higher incidence of complications in untunneled catheters may be caused by differences in patient characteristics and risk factors for infection. All these factors contribute to the finding that the incidence of catheter-related complications can vary widely between the types of catheters used and between dialysis facilities [7]. Therefore, a comparison on the outcome of untunneled catheters in one center with that of another center is not reliable as was recently clearly pointed out by Lund *et al*. [24].
It is not completely clear why tunneled cuffed catheters have a lower risk for infection. It is possible that the fixation of tunneled cuffed catheters is better through the use of a subcutaneous cuff adhered to these catheters in the subcutaneous route and that bacterial migration from the exit-site to the venous entry site is impeded [25]. A recent meta-analysis has clearly demonstrated that cuffing and tunneling of catheters reduces the risk for catheter-related bacteremia by 44-77% [26]. However this analysis only included non-hemodialysis catheters.

TIP DESIGN AND CATHETER LENGTH

Many different catheter types are available and most catheters are offered in multiple lengths. Both untunneled and tunneled cuffed catheters are available in silicon and different polymer plastics. However, limited data are available on what catheter type and material are best. For characterizing catheters, flow curves are often performed in static in vitro models with blood-like substances, not taking into account the possibility of coagulation and pulsatile flow. Furthermore, no model is available for the interdialytic period when the catheter is locked but remains in the blood stream. So far none of the clinical trials has shown a major difference between different catheters [27;28].

Geometry and tip design

The geometry and tip design of catheters have been determined mainly by methods of trial and error. Multiple side holes were thought to be necessary to secure sufficient inflow in case of obstruction of some side holes or when a catheter was placed close to the vessel wall. However, side holes can induce thrombosis because they often have an irregular surface [29]. Furthermore, the diameter of the holes is not adapted to actually required flow rates. Despite the various types of catheters available, studies on the influence of tip construction on fluid dynamics are scarce.

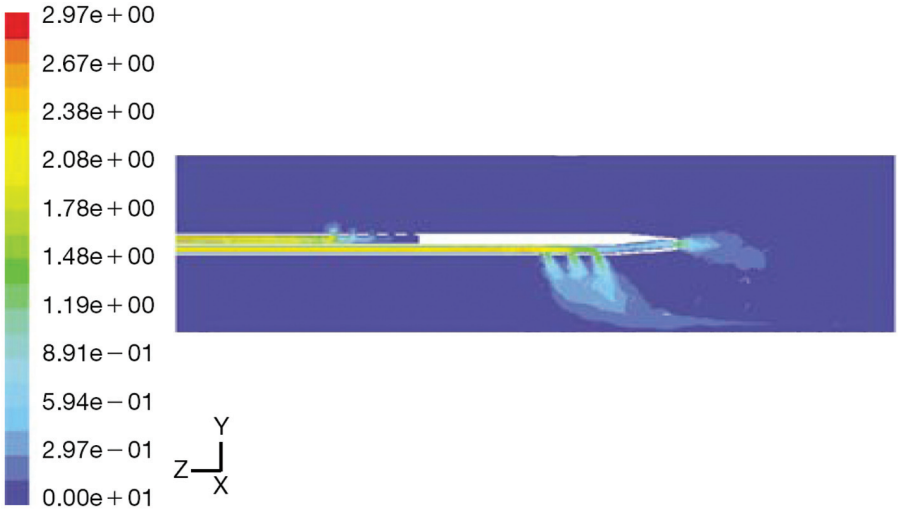

Figure 3.
Computer model for estimation of flow distribution through a catheter with multiple side holes. Scale on the left shows flow speed.

Recently, De Wachter *et al*. [30] presented a study on the hemodynamics of a dual lumen hemodialysis catheter with 5 arterial and 3 venous side holes (Gamcath®, Joka Kathetertechnik, Germany). A computer flow model was used simulating a blood flow of 300 ml/min through the catheter while placed in a 3 cm wide tube. The sequential placement of the arterial holes was demonstrated to be the reason why mainly the first available hole is employed to draw the blood into a catheter. The distal holes of the arterial side appeared to have a low flow zone, suggesting an increased risk of thrombus formation in clinical use (figure 3). Likewise, at the venous side the effectiveness of the multiple side hole design was questioned because the first two side holes appeared to be greatly underemployed. At the most proximal venous side hole (closest to the hub), some of the blood was even drawn into the catheter due to the high difference in velocities between the fluid in the catheter and the vein. Another disadvantage of multiple side holes is that locking solutions can easily dissolve from the tip. The authors concluded that most currently available temporary catheters can be improved to optimize hemodynamics and reduce dysfunction by reducing the number of side holes. Currently, we are using this computer model to analyze different catheter and catheter tip designs to try to determine the optimal tip construction. Preliminary data from this model reveal that double lumen open shotgun tips are optimal and that a single large side hole is probably sufficient.

The relevance of these findings is supported by the outcomes of two recent clinical trials. Oliver *et al*. [31] compared a 12-french tapered tip, multiple side hole catheter with a 13.5-french open shotgun tip catheter. They demonstrated that effective blood flow was higher with the shotgun tip catheter and that there was less necessity for reversal of the lumen polarity, a well known cause of high recirculation rates.
Recently, a randomized study comparing 30 consecutively inserted untunneled femoral catheters was completed [31]. Patients were randomized either to a 20- or 24- cm double-lumen catheter with an open shotgun tip (Niagara®, Bard, Salt Lake City, Utah, USA) or to a 20 cm catheter with a tapered tip (Gamcath®). Recirculation rates were measured at a blood flow of 200, 250 and 300 ml/min with blood-lines situated normally as well as after the reversal of pools.A benefit was demonstrated concerning effective blood flow, recirculation rates and early failure rates for the shotgun tip catheter.
For tunneled cuffed catheters, two prospective randomized studies of interest have been performed. Trerotola et al. randomized 64 patients to the 14 Fr Ash-split catheter and 68 to the 14.5 Fr Opti-flow [27]. Although the authors concluded that the Ash-split catheter had a better survival, the differences seemed to be caused completely by insertion problems (kinking) and manufacturing faults (broken hubs).
There were no differences in catheter-related bacteremia and late flow problems despite large differences in tip construction. Richard et al. compared 38 Ash-split, 39 Opti-flow, and 36 Tesio catheters [28]. Tesio catheter mean insertion time (42 min) was significantly longer than that of Ash-split (29 min) or Opti-flow (30 min) catheters. There were more insertion complications related to Tesio catheters. Mean flow rates and catheter-related infections were not significantly different among the catheter groups. From these studies in tunneled catheters, it can be concluded that double lumen catheters are preferred over two single lumen catheters and that, currently, no double lumen catheter has shown to be superior to an other.
In conclusion, for untunneled catheters there are good data to support that 11-12 Fr catheters with a multiple side hole design should be replaced by a double lumen open shotgun tip design with a larger diameter and no more than one side hole.
For tunneled cuffed catheters, one should probably choose a double lumen catheter for ease of insertion. It has not been shown convincingly that one cuffed catheter design is superior, provided that they have at least a diameter of 14 Fr. Therefore, physicians' experience and cost should play an important role.

The optimal length of the catheter

The current recommendation of the NKF-DOQI is that a femoral catheter should be at least 19 cm long to minimize recirculation [3]. In the aforementioned trial was shown that 24 cm shotgun tip catheters have even lower recirculation rates compared to 20 cm catheters (0 vs 5%). Also direct dysfunction was lower, probably because longer catheters have a better capability to reach the inferior vena cava. Thus, for femoral use double lumen open shotgun tip catheters of at least 24 cm are recommended [31].
For untunneled and tunneled subclavian and jugular catheters data are less clear. NKF-DOQI guidelines recommend placement of a catheter with the tip adjusted to the level of the caval atrial junction or into the right atrium to ensure

optimal blood flow. For untunneled catheters, the catheter length and diameter should be adjusted to the size of the patient. Twardowski et al. [32] determined the exact distance from
an insertion site to the right atrium by magnetic resonance imaging of the dimensions of the venous system of the chest in 31 adult volunteers and correlated them to anthropometrical measurements. The best overall correlations of the lengths and diameters of the large upper body veins were with the body surface area.
A table was made to help with the selection of the total catheter length and diameter in relation to the body surface area and insertion site. In general, in patients with a body surface area of 1.5 to 2.0 m2 a 12-15 cm catheter should be selected for the jugular vein in the low right position and a 15-19 cm catheter for the left jugular vein.
A 14 to 17 cm catheter should be used for the right subclavian vein and a 17 to 22 cm catheter for the left subclavian vein.
For the preferred length of tunneled cuffed catheters no guidelines are available. In our experience, for the right jugular position (tip to hub) 28 cm are needed for appropriate atrial placement and an adequate tunnel length. For the left jugular vein we use a 32 cm catheter.

CATHETER MATERIALS AND COATINGS

In vitro data on the biocompatibility of polymers used in catheter manufacturing, namely silicon and polyurethane, are conflicting [33;34]. Likewise, in small randomized trials comparing tunneled cuffed catheters of different materials and construction, no clear benefit of one particular material was found [35]. It might be that silicone catheters are more prone to construction failures because of the difficult manufacturing process necessary [36].
Promising progress is made with coating of catheters. In ICU patients catheters coated with antibiotics, silver or heparin reduce the number of infections substantially. In a recent review, however, only heparin-coated catheters were considered to be cost-effective [10]. Studies on hemodialysis catheters have been disappointing so far [37]. A problem with bonding of hemodialysis catheters is that they are often needed for a longer period of time and the substance impregnated or bonded on catheters can disappear over time.

GUIDELINES FOR INSERTION PROCEDURES AND POST PROCEDURAL CHECKS

Complications can be minimized when insertion is performed or supervised by an experienced physician. Both untunneled and tunneled cuffed catheters can be safely inserted under local anesthesia by nephrologists or radiologists [24;38]. The procedure should be strictly aseptic. Light sedation can be of benefit in anxious patients. Ultrasound-guided cannulation has proven to be superior to landmark-guided cannulation and is therefore recommended by the NKF-DOQI [3].Femoral catheters can be inserted using a blinded percutaneous Seldinger technique, but for femoral catheters it has also been shown in dialysis patients that procedure time can be significantly shortened with the use of ultrasound guidance [39]. The first attempt success rate increased by 30% and accidental arterial puncture decreased by about 10% [40].

For jugular and subclavian vein cannulation there is also extensive evidence for the use of ultrasound localization of the vein before puncture as well as the use of real time ultrasound guided cannulation [16;41]. The risk of complications such as pneumothorax, arterial puncture and fausse route can be decreased to less then 2% and procedure times are shortened. However, long term patency and the risk of infection were not improved in these trials.
It has been demonstrated that patency rates and recirculation are affected by correct positioning of the tip of the catheter [42;43]. Preferably, the tip should be at or just below the caval-atrial junction. Fluoroscopy during positioning has been advised by radiologists but is not always available to nephrologists and has not turned out to be beneficial. Using the knowledge from the study of Twardowski et al. on the correlation between BSA and large vein sizes as discussed in the paragraph on catheter length, correct placement of tunneled catheters is possible without fluoroscopy [32].
After insertion of tunneled cuffed catheters a chest X-ray is mandatory for evaluating complications and correct positioning of the tip. However, when untunneled jugular catheters are inserted with ultrasound localization, the procedure is uncomplicated and straightforward, the blood flow is good, and there are no post procedural complaints of the patients, there is convincing evidence that dialysis can be started safely without the use of a chest X-ray. This can offer substantial savings [43-45].

DRESSINGS, ANTIMICROBIAL EXIT-SITE APPLICATIONS AND LOCKING SOLUTIONS

All hemodialysis catheter manipulations should be performed by carefully instructed dialysis staff. At every dialysis session, the exit-site should be cleaned with a chlorhexidine-containing solution as this can reduce infectious complications by 49% compared to the use of povidone iodine [46]. It has clearly been shown that non-occlusive dry gauze dressings should be used for covering the exit-site [47]. Recently, antimicrobial ointments have been introduced. Mupirocin ointment and a polysporin triple antibiotic ointment have been shown to reduce the risk of infectious complications by 70 to 80% [48;48-50]. Therefore, mupirocin ointment has been advocated in the latest NKF-DOQI guidelines. However, widespread introduction could lead to the development of mupirocin resistance which may limit its application in the future [51;52].
Catheters have to be locked with a solution for the interdialytic period. Traditionally, heparin is installed but there are no studies to support this practice. Moreover, an increasing number of reports are published showing that leakage of heparin from the tip of the catheter can cause unintentional systemic anticoagulation and clinically relevant bleeding episodes [53;54]. Antimicrobial locking solutions could be an attractive alternative and will emerge into clinical practice in the near future. It is known from *in vitro* studies that solutions containing antibiotics can prevent biofilm formation on foreign surfaces [55]. But also the use of antibiotics in solutions for interdialytic locking of catheters can result in severe side effects caused by leakage from the tip resulting in continuous systemic levels of the antibiotic. Dogra et al. [56] demonstrated in a randomized trial that gentamicin in a lock solution reduced the number of incidents of catheter-related bacteremia but also caused irreversible hearing problems because

high plasma levels of gentamicin occured. Trisodium citrate (TSC) has been advocated for locking because it provides local anticoagulation. Ash et al. [57] reported their experience with a hemodialysis patient cohort of 70 patients with 60% tunneled cuffed catheters. After the introduction of TSC 23-47% for catheter locking they observed a decline of 4.5 to 0% patients having a bacteremia. The utilization of urokinase for catheter flow problems also decreased significantly. Additional advantages of TSC are that it prevents unforeseen systemic anticoagulation and is less expensive than heparin. However, an important concern has risen over an accident using TSC for catheter locking. In this particular case, a large amount (over 10ml) of TSC was accidentally injected by a physician not aware of the potency of the solution, which stresses the importance of a thorough protocol for these solutions [58].

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2 Aim and outline of the thesis

The objective of the studies presented in this thesis was to reduce hemodialysis catheter-related complications by studying the influence of the following issues.

CANNULATION SITES AND WHEN SHOULD A CATHETER BE TUNNELED

In **Chapter 3** we address the best cannulation site once the time period a hemodialysis catheter is needed has been estimated. According to the NKF-DOQI guidelines, untunneled femoral catheters should not be left in place for more than 5-7 days because of the high risk of infections. For untunneled jugular catheters the opinion is not to use these for more than 3 weeks and use an untunneled jugular catheter for the longer time periods. However no clinical studies support these time limitations. We analysed the outcome of hemodialysis catheters to address the issue of timing and catheter choice. In **Chapter 4** we describe the effect of a novel design jugular catheter on catheter-related complications and addressed the time recommendations found in the previous study, including the question when a hemodialysis catheter should be tunneled.

CATHETER MATERIALS, CONSTRUCTION AND TIP DESIGN

Hemodialysis catheter related complications can be caused by imperfect catheter constructions. Especially the construction of untunneled jugular catheters could be an important reason because these catheters can not be fixated well and have an upward directed exit-site, a well known risk factor for catheter-related infections.
Recently a for patients more comfortable untunneled jugular catheter with better properties concerning fixation and exit-site direction has become available.
In **Chapter 4** we study the influence on infectious complications of using this novel design precurved jugular hemodialysis catheter in a clinical study.
It is not clear whether silicone or polymers like polyurethane should be the preferred material for hemodialysis catheters. Catheter fractures have been reported, especially with silicone catheters. The reason for these fractures is unknown and it is not clear whether catheter material is relevant. In **Chapter 5** we describe the construction and potential flaws in the manufacturing process from a fractured silicone hemodialysis catheter by performing an extensive scanning electron microscopy study and using energy-dispersive X-ray spectral analysis to determine the components of the catheter.
The geometry and tip design of catheters have been determined mainly by methods of trial and error. Multiple side holes were thought to be necessary to secure sufficient inflow in the case of obstruction of some side holes or when a catheter was placed close to the vessel wall. However, side holes can induce thrombosis because they often have an irregular surface. Despite the various types of catheters available, studies on the influence of tip construction on fluid dynamics are scarce.
In the second study presented in **Chapter 5** we performed an in vitro study on the fluid dynamics of four different types of tunneled and untunneled catheters. To determine the influence of side holes, catheters were studied with open and closed side holes.

LOCKING SOLUTIONS

Catheters have to be locked with a solution for the interdialytic period. It is well known that locking solutions leak out from the tip of the catheter, but the clinical implications of this feature are not clear. Traditionally, heparin is installed but there are no studies to support this practice. Heparin might be causing clinical problems because of unintentional systemic anticoagulation. Local acting antimicrobial locking solutions could be an attractive alternative. Low and high concentrations of trisodium citrate (TSC) have been advocated as locking solution because it provides local anticoagulation and might have antimicrobial properties. Additional advantages of TSC are that it gives no unforeseen systemic anticoagulation and is less expensive than heparin. However, the optimal concentration of TSC remains to be determined. In **Chapter 6** we describe the antimicrobial properties of 4 different concentrations of TSC in vitro, using two classical antimicrobial susceptibility tests. From this study we derived the optimal concentration for a catheter locking solution to be used in a multicenter double blind randomised controlled trial. Results of this trial are also described in **Chapter 6**.
In this study we also describe the clinical relevant complications of locking solution leakage from the catheter tip.

3 Comparison of outcome of temporary catheters at different sites and tunneled cuffed catheters

Compared to tunnelled cuffed haemodialysis catheters, temporary untunnelled catheters are associated with more complications already within 2 weeks of use.

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ABSTRACT

Background. Comparison of outcome of untunneled catheters (UC) and tunneled cuffed catheters (TCC) is difficult because they are usually used for different patients and conditions. The aim of the present study is to compare the outcome of TCC with UC limiting as much as possible the influence of confounding factors. The second purpose was to see whether our results support the time recommendations for maximum use of UC outlined in the NKF-DOQI guidelines.

Methods. Catheter and patient characteristics, catheter-related complications and all cultures taken from hemodialysis catheters inserted during a three year period were collected.

Results. We analyzed the outcome of 272 catheters (149 patients, 11612 catheter days, 37 TCC and 235 UC). Patients with an UC suffered more often from acute renal failure (40% vs 8% for TCC, $p<0.001$), their hospitalization rates were higher (54% vs 14%, $p<0.001$) and coumarins were used less (11 vs 27%, $p<0.01$). Rates of preliminary removal were 1.8 per 1000 catheter-days for TCC, 35.3 for untunneled femoral catheters (UFC) and 17.1 for untunneled jugular catheters (UJC). Infection rates were 2.9 per 1000 catheter-days for TCC, 15.6 for UJC and 20.2 for UFC. Hospitalization, was an independent risk factor for an adverse outcome and more apparent in patients with an UC. After correction for patient differences, the strongest risk factor for preliminary removal (RR 9.69, $p<0.001$) and infection (RR 3.76, $p<0.001$) was having an UC inserted. Already within two weeks actuarial and infection free survival were better for TCC ($p<0.05$ vs all separate groups).

Conclusion. According to our results, a TCC should be used whenever it can be foreseen that a hemodialysis catheter is needed for more than 14 days.

INTRODUCTION

Vascular access for hemodialysis treatment is best achieved with an arteriovenous fistula or arteriovenous graft. Tunneled cuffed hemodialysis catheters (TCC) are used for long-term vascular access in a small proportion of patients mostly because opportunities for an arteriovenous access are exhausted. However, a significant number of patients requires a temporary vascular access because of acute renal failure, slow maturation or failure of their permanent arteriovenous access or as bridging to transplantation or peritoneal dialysis. In these situations, untunneled catheters (UC) are used when a catheter is needed for only a short period of time and TCC for longer periods. UC are relatively small bore (11-13 Fr) catheters and have no cuff adhered to the catheter. These can be inserted with relative ease by a bed-side procedure under local anesthesia without the formation of a subcutaneous tunnel and are usually intended for a relatively short period of time. In current practice the use of catheters for hemodialysis treatment is substantial. From recent data of the Dialysis Outcome and Practice Patterns Study (DOPPS), it is recognized that 15-50% of patients in Europe and 60% of patients in the US start hemodialysis treatment with a catheter as primary access [1]. This widespread use of catheters implies an enhanced risk for catheter-related complications, particularly catheter-related infections. Observational data suggest that these risks are higher for temporary UC compared to TCC and this is also reflected in guidelines[2]. Recently, the updated NKF-DOQI guidelines recommended that when it can be anticipated that a catheter will be needed for more than three weeks, a TCC should be inserted [3]. Inserting TCC, however, requires more experience, prolonged procedure time and special skills of the operator. In addition, removal is hampered by growth of the subcutaneous tissue into the cuff . These drawbacks for the use of TCC might explain the observation in the DOPPS that UC are still widely used. In incident hemodialysis patients, 48% of catheters in the US and 75% of catheters in Europe are untunneled and even in prevalent patients over a third of all catheters are untunneled [1]. As was pointed out recently, there are limited data available in the literature comparing the outcome of UC and TCC [4].

Reported bacteremia rates vary from 3.8-6.5 per 1000 catheter-days for UC and 1.6-5.5 for TCC [5-9]. In these studies, catheter care protocols and the definition of complications differ. In addition, because UC and TCC are used for different clinical situations, the higher incidence of complications in UC may be caused by differences in patient characteristics and risk factors for infection. These factors all contribute to the finding that the incidence of catheter-related complications can vary widely between types of catheters used and dialysis centers [10]. Therefore, comparison of outcome of UC in one center with TCC in another center is not reliable as was clearly pointed out by Lund *et al* [11]..

The aim of the present study was to compare the outcome of TCC with UC limiting as much as possible the influence of confounding factors. The second purpose was to see whether our results support the time recommendations for maximum use of UC outlined in the NKF-DOQI guidelines.

SUBJECTS AND METHODS

Patients and data collection

We analyzed all hemodialysis catheters inserted at the dialysis department of an academical teaching hospital from January 1st 1997 to January 1st 2000. On average, 60 hemodialysis patients are treated in our unit, 10% are acute patients and 25% of patients depend on a catheter for vascular access. Follow-up on inserted catheters was done from insertion to removal and in case of persistent patency up to July 1st, 2000. Data on all inserted catheters and catheter-related complications at follow-up were entered prospectively in a computerized patient data system by the caring nephrologist and dialysis nursing team. The decision on the type of catheter and place of insertion was left to the physician responsible for the patients' care at time of insertion.
Reasons for catheter removal were entered in the database: elective removal, exit-site infection or bacteraemia, dysfunction or accidental removal. In case of uncertainty the caring nephrologist was consulted. Catheters were evaluated for type, place of insertion, time of insertion, duration of use and reason for removal. All cultures of blood and exit-sites taken from the patient during the period that a catheter was in place were collected from the computerized data system of the department of microbiology. Baseline patient characteristics and demographical data were collected at time of insertion.
In addition, hospitalization for non catheter-related reasons at any time a catheter was in place was analyzed as separate risk factor for adverse outcome[10]. Acute renal failure was defined as dialysis dependency for less then three months which was not the result of slowly progressive renal insufficiency. All other patients where considered having chronic renal failure including patients referred because of failing peritoneal dialysis treatment. Patients after renal transplantation were only considered having chronic renal failure if they needed dialysis treatment because of chronic rejection.
Data on two catheters (both untunneled jugular catheters) were lost to follow-up because of transferal to an other dialysis center. Three catheters (two femoral and one subclavian untunneled catheter) were excluded from analysis due to insufficient data.
These were excluded from the analysis. Catheters, intended to be used only once (almost exclusively untunneled femoral catheters) were not included in the analysis.

Catheters, catheter care protocol and catheter outcome assessment

For femoral, we used straight dual-lumen polyurethane catheters of 20 cm, for the right subclavian site 15 cm and for the left subclavian position 20 cm (Quinton (Seattle, WA, USA); n=18 and Gamcath (Gambro, Hechingen, Germany); n=113).
For the internal jugular position we used the same catheters with curved extensions (Quinton n=15, Gamcath n=89). For TCC we used Neostar Circle-C (Horizon Medical Products, Atlanta, GA, USA; n=24), PermCath (Quinton Instruments, Bothell, WA, USA; n=5), Tesio twin-cath (n=3) and Ash-split (Medcomp, Medical Components Inc., Harleysville, PA, USA; n=5).
All catheters were inserted under local anesthesia and strict asepsis, and sutured to the skin. Catheters were only used by experienced dialysis nurses or nephrology staff, using sterile gloves and masks. The semi-occlusive transparent dressings we used, were inspected every dialysis session and changed at least once a week, the exit-site being

cleansed with a povidone-iodine solution. Before removing the caps, the catheter hubs were disinfected with a chlorhexidine solution (2.5%). After dialysis all catheters were locked with unfractionated heparin (5000 U/ml) with a volume equivalent to the internal volume of the lumen noted on the catheter. Catheters were used for hemodialysis exclusively.
Catheter-related bacteremia was defined as fever or cold chills with positive blood cultures and no other obvious cause of infection. When a catheter-related bacteremia was established, the catheter could be left in place in case of good clinical response on initiation of antibiotic treatment. No catheter exchange procedures for catheter-related bacteremia were performed. A catheter-related exit-site infection was considered to be present on clinical grounds by the caring nephrologist, a culture of the exit-site was taken and treatment with antibiotics had been started.
In accordance to national guidelines, the minimal acceptable Qb was 200 ml/min, the target was 250 ml/min. The target for dialysis efficiency was a Kt/V of at least 1.2 per treatment. When the minimal acceptable blood flow was not achieved or when the catheter was occluded, urokinase, 10.000U/ml during 15 minutes, was installed with a volume equivalent to the internal volume of the lumen. In general, when Qb improved but 200 ml/min was not achieved, the procedure could be repeated, otherwise the catheter was removed or exchanged over a guide wire.

Statistical analysis

Statistical analysis was performed with SPSS software 9.0 (SPSS Inc., Chicago, Ill, USA). Non parametric tests for two (Mann-Whitney U test) and multiple continuous variables (Kruskal-Wallis test) were used. For comparing binary and categorical variables Chi-square and Fisher's exact tests were applied where appropriate. ANOVA was used to compare age and time on dialysis between multiple groups. Kaplan-Meier survival curves were constructed to analyze the patency rates and infectious complications. Functional catheters at the end of the observation time and catheters removed because they were not needed anymore were analyzed as censored values.
Curves were constructed for all patient and catheter characteristics mentioned in table 1. The log rank test was used to compare groups and identify individual risk factors associated with a preliminary removal or catheter-related infection.
At an individual two-sided P value of < 0.1, the factor was included to fit a Cox-regression model. We have included male sex, acute renal failure, time on dialysis, hospitalization and having an UC inserted in the final model. We used a forward stepwise conditional technique to identify the factors independently associated with catheter failure and infection. R-square of linear regression was estimated for infection free survival and overall patency curves. Actuarial catheter survivals at 14, 21 and 28 days were counted with the use of life tables and significance was calculated with the log rank test for the individual time periods. Differences were considered statistically significant for p less than 0.05.

RESULTS

A total of 272 catheters (11612 catheter days) in 149 patients (82 male, 57 female) were included in the final analysis. There were 83 untunneled femoral catheters (UFC) inserted, 104 jugular (UJC) and 48 subclavian (USC). Of 37 TCC, 35 were jugular and 2 were femoral. There were no significant differences in outcome between left and right-sided catheters and between the different types of catheters. Patients with more than one catheter inserted were more likely to be chronic patients and on dialysis for a longer period of time and less likely to be hospitalized during the period they had a catheter placed.

In our study the risk for an adverse outcome or infection for second or more insertions was not increased (RR 1.10, 95% CI 0.75-1.62 P=0.62) and therefore these catheters were not analyzed separately. Patient and catheter characteristics are given in table 1.

Of patients who had a TCC inserted, 92% was on chronic haemodialysis treatment in contrast to patients with an UJC (62%, p<0.001) and to the group of all UC combined (60%, p<0.001). Patients with UC were characterized by higher hospitalization rates for non catheter-related reasons compared to TCC (54% vs 14%, p<0.001). Also, patients with UC concerned patients admitted to the intensive care more often (p<0.01). Furthermore, 27% of TCC were inserted with the use of a guide wire exchange procedure (p<0.01) and more patients with a TCC were on coumarin treatment (11 vs 27%, p<0.01). Other differences in patient characteristics were not significant.

Table 1. Catheter and patient characteristics

Catheter characteristics	Untunneled catheters				TCC
	femoral	jugular	subclavian	total	
No. of catheters	83	104	48	235	37
No. of catheter-days	793	3209	1492	5494	6118
Right sided insertion (%)	53	84	63	69	87
Guide wire exchanges (%)	5	9*	21	10*	27*
Patient characteristics					
Age (mean ± SD)	60.3 ± 15.9	61.0 ± 13.8	62.9 ± 15.6	61.1 ± 16.0	62.5 ± 13.0
Gender male (%)	55	66	60	61	51
Race (%)					
caucasian	70	71	83	73	70
black	19	18	15	18	22
other	11	11	2	9	8
Cause of ESRD (%)					
diabetes	18	24	13	20	30
renovascular	16	20	29	20	11
polycystic disease	2	8	4	5	16
glomerulonephritis	16	13	13	14	8
HIV	2	1	2	2	0
other	41	24	31	31	27
unknown	5	10	8	8	8
Acute renal failure (%)	42	38**	44	40**	8**
Diabetes mellitus (%)	23	32	25	27	35
Hospitalization at all (%)	68	42 †	52	54 †	14 †
general ward	43	31	29	35	14
intensive care	25	11	23	19	0
Time on dialysis (mo ± SD)	15.8 ± 24.9	13.8 ± 25.1	15.6 ± 25.9	14.9 ± 25.1	23.5 ± 29.7
Immunosuppressive drugs	15	14	6	12	11
Coumarines (%)	12	8 ‡	15	11 ‡	27 ‡
Sau nasal carrier (%)	45	48	49	48	32
Malignancy (%)	15	9	8	11	3

Abbreviations: TCC, tunneled cuffed catheters; SD, standard deviation; ESRD, end-stage renal disease; Sau, Staphylococcus aureus

** P<0.01*

*** P<0.001*

† P<0.001

‡ P<0.01

CATHETER OUTCOMES

Of 235 UC inserted, 128 (54%) were removed because they were not needed anymore compared to 26 (70%) of TCC. In contrast, 107 (46%) UC had to be removed for a complication compared to 11 (30%) TCC (p<0.001 by log rank analysis). Catheter and patient characteristics are shown in table 2.

Table 2. Characteristics of premature catheter removal

	Untunneled catheters				TCC
	femoral	jugular	subclavian	total	
No. of Catheters	83	104	48	235	37
Removal for all complications	28 (34%)	55 (53%)	24 (50%)	107 (46%)	11 (30%)
per 1000 catheter-days	35.3	17.1	16.1	19.5	1.8
Reason for premature removal					
infection	12 (43%)	37 (67%)*	3 (13%)*	52 (49%)	6 (55%)*
flow problem	13 (46%)	16 (29%)	19 (79%)	48 (45%)	3 (27%)
mechanical / fracture	3 (11%)	2 (4%)	2 (8%)	7 (7%)	2 (18%)

NOTE. Values expressed as number (percent) unless noted otherwise.
Abbreviations: TCC, tunneled cuffed catheters
** P<0.05 for comparison between untunneled subclavian and untunneled jugular and TCC*

The rate for preliminary removal per 1000 catheter-days was lowest for TCC (1.8) and highest for UFC (35.3). UJC and USC had similar rates (17.1 and 16.1 per 1000 catheter-days) but were also higher than TCC. Reasons for premature removal differed slightly but not significantly between UC and TCC. Infection was the primary reason (49% for UC and 55% for TCC). Considering untunneled catheters only, USC were removed less because of infection but more for persistent flow problems or mechanical complications, compared to both UFC (p<0.05) and UJC (p<0.01) catheters. Log rank analysis of survival curves showed better patency rates for TCC compared to any of the untunneled groups (p<0.001) adjusted for hospitalization. Of UC, outcome of UFC was significantly worse compared to USC (p<0.05) and UJC (p<0.01) (figure 1a). Cumulative hazard-ratio analysis of adverse outcome showed a linear appearance for all catheter groups suggesting a risk of adverse outcome constant over time (test for linearity R2 > 0.8 for all groups).
To relate the results to the time recommendations in the NKF-DOQI guidelines, we calculated the patency rates at 14, 21 and 28 days. Actuarial catheter survival was best for TCC, 95% at 14 days, 95% at 21 days and 95% at 28 days.

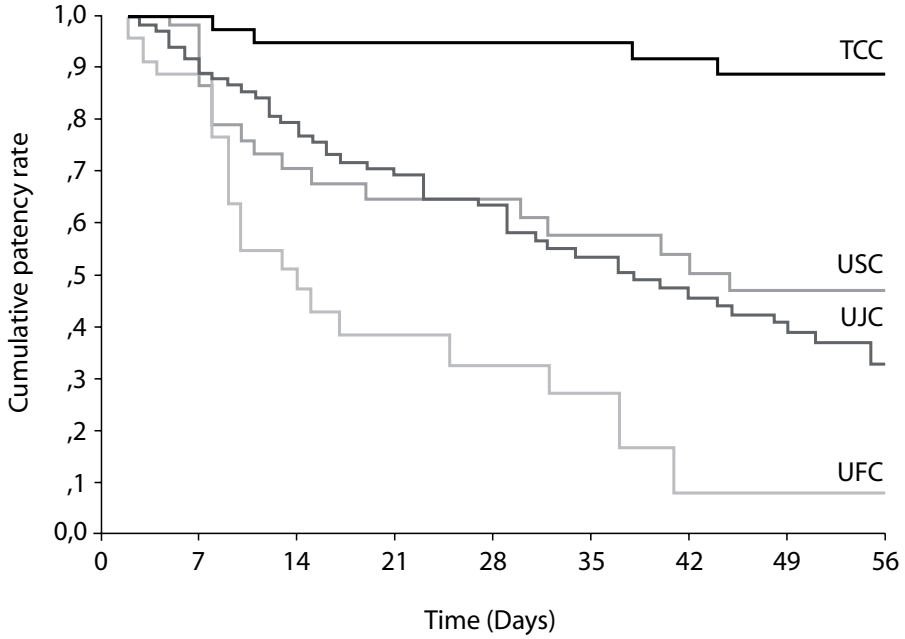

Figure 1a. *Kaplan-Meier curves of total survival of tunneled cuffed catheters (TCC) (——) compared to untunneled jugular (UJC) (——) (p<0.001 by log rank statistics), untunneled femoral (UFC) (——) (p<0.001) and untunneled subclavian catheters (USC) (——) (p<0.001. Tick marks indicate censored catheters.*

The survival for UFC was significantly lower for any time point compared to TCC (42% at 14 days, 37% at 21 days and 32% at 28 days, p<0.001 for all periods) and UJC (75% at 14 days, 69% at 21 days and 58% at 28 days, p<0.05 for all periods). Importantly, TCC had also better survival rates at all time periods compared to UJC (p<0.01 for all periods by log rank testing) (figure 2a).
As patient characteristics differed between the catheter groups, risk factors for adverse outcome were analyzed. After univariate analysis, male sex (RR 1.73), acute renal failure (RR 1.75), hospitalization (RR 2.48) and having an UC inserted (RR 9.44) were significant associated with preliminary removal. The strongest factor predicting an adverse outcome was having an UC inserted (RR 9.69; 95% CI 4.25-22.08 P<0.001, after correction for hospitalization). When only jugular catheters were compared, the risk of preliminary removal for UC remained almost tenfold increased (RR 9.39; 95% CI 3.96-22.28 p<0.001, after correction for hospitalization). Hospitalization was the only other independent factor (RR 2.41; 95% CI 1.60-3.61 p<0.001).

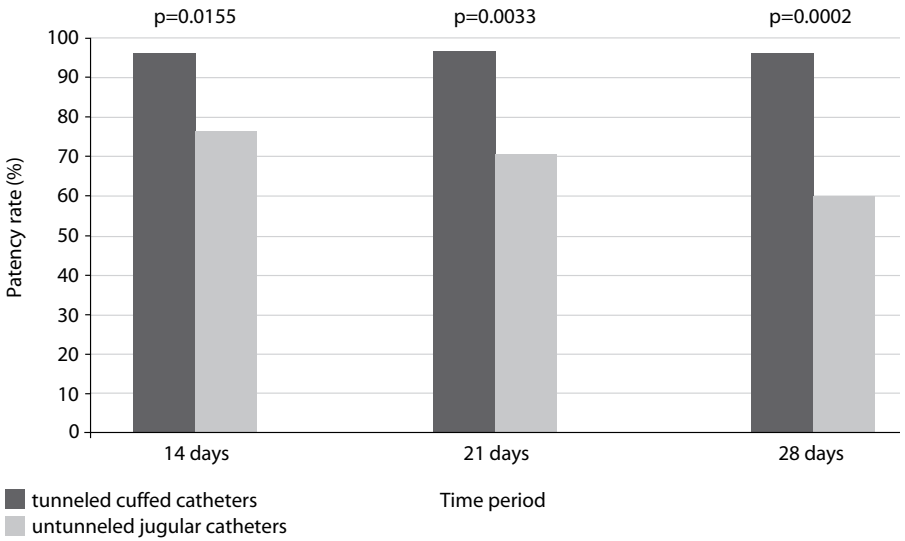

Figure 2a. *Patency rates at 14, 21 and 28 days of tunneled cuffed catheters compared to untunneled jugular catheters.*

INFECTIOUS COMPLICATIONS

A total of 35 episodes of catheter-related bacteremia (CRB) occurred in 31 catheters in 27 patients; in 8 patients an exit-site infection preceded CRB. There were 45 episodes of solitary exit-site infections. Differences in CRB and exit-site infection rates within the catheter groups are presented in table 3.

Table 3. Characteristics of catheter-related infections

	Infection rates per 1000 catheters-days		
	Exit-site infection	CRB	Total
TCC	1.3	1.6	2.9
All untunneled	8.2	4.6	12.8
femoral	12.6	7.6	20.2
jugular	10.0	5.6	15.6
subclavian	2.0	0.7	2.7

Abbreviations: TCC, tunneled cuffed catheters; CRB, catheter-related bacteremia

Infection rates for TCC (2.9 per 1000 catheter-days) were significantly lower compared to UC (12.8 per 1000 catheter-days, p<0.001 by log-rank testing), especially to UJC (15.6 per 1000 catheter-days, p<0.001) and UFC (20.2 per 1000 catheter-days, p<0.01). CRB rates per 1000 catheter-days showed analogous results (table 3).
The probability of infection free survival was best for USC and TCC (91% at 14 days, 89% at 21 days and 89% at 28 days) (figure 1b).

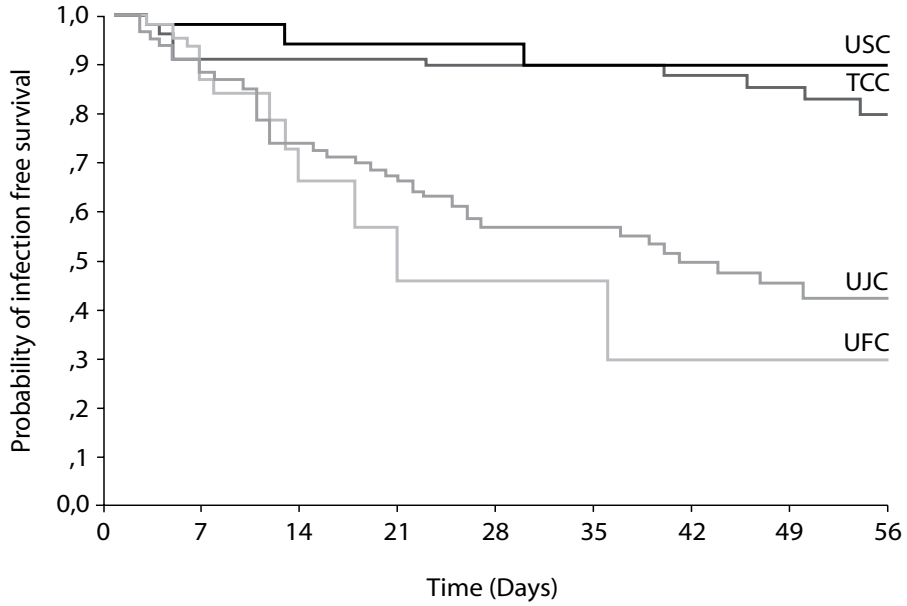

Figure 1b. *Kaplan-Meier curves of infection free survival of tunneled cuffed catheters(TCC) (——) compared to untunneled jugular (UJC) (——) (p<0.01 by log rank statistics), untunneled femoral (UFC) (——) (p<0.01) and untunneled subclavian catheters (USC) (——). Tick marks indicate censored catheters.*

For UJC the probability of infection free survival was significantly lower for any time point compared to TCC (UJC; 73% at 14 days, 64% at 21 days and 56% at 28 days; p<0.05 for all periods, figure 2b). The rates for CRB free survival were also significantly better for TCC.

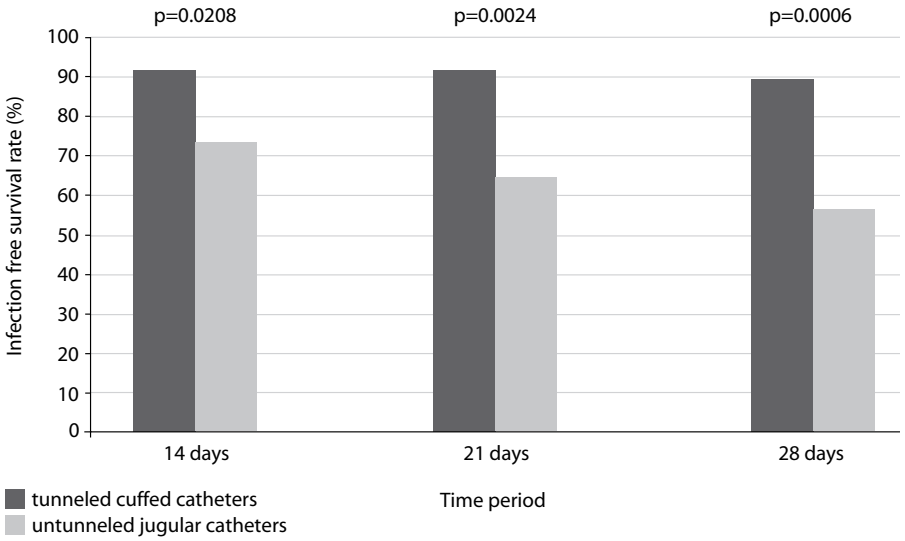

Figure 2b. *Infection free survival rates at 14, 21 and 28 days of tunneled cuffed catheters compared to untunneled jugular catheters.*

Risk factors for infection differed only slightly from risk factors for preliminary removal. Again, the only independent risk factors for infection were having an UC (RR 3.03, 95% CI 1.54–5.94, P=0.001) and hospitalization in the week before the infection occurred (RR 2.72, 95% CI 1.75–4.22, P<0.001). Untunneled and tunneled jugular catheters were compared after correction for differences in patient characteristics.
The strongest risk factor for infection (RR 3.76, 95% CI 1.88-7.51 P<0.001) or CRB (RR 3.07, 95% CI 1.08-8.74, P<0.05) was having an untunneled jugular catheter.
In 48% of cases cultures yielded gram-positive microorganisms, predominantly *Staphylococcus aureus or Staphylococcus epidermidis*, in 36% it concerned gram-negative microorganisms. The remaining cultures revealed multiple microorganisms or yeasts.

DISCUSSION

Our study demonstrates that TCC had significant better survival and lower risk for infection compared to UC as early as two weeks after insertion. We have shown that the risk for an adverse outcome increases linearly over time. This implicates that almost all catheters for hemodialysis treatment should be tunneled. The unique feature of our study is that we performed a single center study and used a similar catheter care protocol by the nursing staff for all catheters. Furthermore, we corrected for differences in patient characteristics that might have interfered with the better outcome of patients with a TCC. This results in a more reliable comparison between catheter groups, compared to previous reports. So far, the current evidence for time recommendations on the use of catheters is from uncontrolled studies not correcting for differences in patient

characteristics. Kairaitis *et al* found in their prospective study on 105, mainly subclavian, UC that 59% of catheters had to be removed prematurely because of a complication. A total of 6.5 periods with CRB per 1000 catheter days were observed [5]. However, only few patient characteristics (age, gender and diabetes) were reported. Furthermore, 75% of catheters were inserted in the subclavian vein and no data are available on the number of right and left sided catheters. In contrast, Oliver et al recently reported a much lower rate of CRB of 3.8 per 1000 catheter-days for UC even including femoral catheters [7]. Patients' characteristics, however, were not described but only analyzed as risk factor for CRB and no data were given concerning patency rates.
In a large prospective study analyzing vascular access infection in 111.383 dialysis sessions, Stevenson *et al* found a relative risk for CRB of 1.9 for UC compared to TCC [2]. However, the major limitation, already recognized by the authors in their discussion, was that no data were available on patient characteristics and sites of insertion and no corrections could be made for these potential confounding factors. Moreover, only 1.6% of all dialysis treatments were performed with the use of an UC suggesting that these catheters were used only in a very specific patient group. In studies investigating TCC only, the incidence of CRB generally is lower (1.3-5.5 episodes per 1000 catheter-days) [5] compared to our results. It is, however, striking to observe the four-fold higher incidence of CRB found in the study by Saad (5.5 periods of CRB per 1000 catheter-days) compared to the study of Little *et al* (1.3 periods of CRB per 1000 catheter-days) while their study design and definition of CRB seemed comparable [6;8]. These differences between catheter studies could well be caused by differences in patients' characteristics or catheter management protocols. From these observations it is obvious that the reported complication rates for UC and TCC in these studies differ widely and can not be used for individual comparison.
In the present study we could demonstrate multiple differences between patients who had an UC or a TCC inserted. In particular, we observed more hospitalizations, an established risk factor for infections, for non catheter-related reasons in patients with an UC. This observation concerning hospitalization as risk factor for adverse outcome confirms the findings of Tokar *et al* [10].
Another important factor influencing the outcome of catheters is the catheter care protocol. It has been shown in randomized studies and recommended in the NKF-DOQI guidelines that the risk for CRB can be reduced with a thorough protocol [3;12]. Even the level of education of the dialysis nurses concerning catheter handling influences the outcome [13]. Studies on catheter-related complications differ widely in these practices and could be an important confounder when comparing patency rates and CRB. In the present study we have tried to exclude these possible confounding factors by using a similar catheter care protocol for all catheters.
To relate our results to the NKF-DOQI guidelines, we focused on the survival and infection rates for the time period of four weeks as UC, especially UJC could be a reasonable alternative to TCC for this period of time [7]. We could demonstrate that even when a catheter is needed for only 14 days, the best survival and lowest infection rates were for TCC. Within two weeks, 25% of UJC had to be removed for a complication and in 27% an exit-site infection or CRB had occurred. Of all TCC only 5% had to be removed for

a complication within two weeks and 9% of catheters were infected. This conclusion is also supported by the observation that the patency curves and the infection free survival curves are close to linear (R-square > 0.8 for all curves). Linearity means that the risk is independent of time, that episodes of infection per 1000 catheter-days can be compared proportional and are valid for every time period [11]. However, earlier use of TCC must be weighted against the more time consuming and difficult insertion and removal of TCC and the higher costs.

It is not completely clear why TCC have a lower risk for infection. One explanation could be that the fixation of TCC can be achieved better by the use of a subcutaneous cuff and that bacterial migration from the exit-site to the venous entry site is impeded [14].

A recent meta-analysis has clearly demonstrated that cuffing and tunneling of catheters reduces the risk for CRB by 44-77%, however this analysis only included non-hemodialysis catheters [15]. UJC are more difficult to fixate properly. Furthermore, they have an upward directed exit-site, an established risk factor for infection in peritoneal catheters [16]. This is probably because debris can accumulate, colonization is promoted and pus can not drain in case of local infection. In addition, preliminary reports on precurved UJC with better possibility for fixation and a downward directed exit-site suggest they can be left in place for a longer period of time with an equivalent risk for infection compared to TCC [17]. USC mostly have a downward directed exit-site and can be fixated more easily. This could explain the lower risk for infection for USC we found compared to UJC, as was already shown in the study on UC by Kairaitis *et al* [5].

An other point that influences the function of catheters is their construction. As TCC have a 2 to 3 Fr larger diameter and Poiseuille's equation dictates that the flow rate is inverse proportional to the diameter to the fourth power, it is clear that there is more reserve in case of partial obstruction for TCC compared to UC. Our study has several limitations. First, the present study represents observational and prospectively stored data and the allocation to any type of catheter was not randomized.

Guidelines should ideally be based on results from prospective randomized studies. However, the need of a large randomized controlled trial could be questioned if our results had supported the time recommendations on the safe use of UC. In the light of current recommendations it is very difficult to conduct a randomized trial comparing TCC and UC and no such trial reports have appeared in the literature so far despite the great number of catheters used worldwide. . Second, like in almost all other catheter studies we included all catheters inserted in patients and not only first episodes. This could lead to repeated tabulation of patients and dependency of catheter episodes. However, in temporary catheters, Oliver et al recently showed that multiple insertions and even guide wire exchanges are not a risk factor for an adverse outcome [7]. For TCC, Little et al could only find an increased risk for an adverse outcome when three or more TCC were inserted [8]. In our study only 3 patients had two TCC inserted and no patient had more then two inserted. Furthermore, the risk for an adverse outcome or infection for second or more insertions in our study was not increased (RR 1.10, 95% CI 0.75-1.62 P=0.62). Third, despite similar protocols for TCC and UC in our center, there is a possibility that more often thrombolytic treatment was used for a dysfunctional TCC and that dysfunctional TCC were left in place longer than

dysfunctional UC because the latter can be exchanged more easily.

However, it is unlikely that dysfunctional catheters regain flow when one or two sessions of intraluminal thrombolytic therapy are unsuccessful [18]. In addition, the acceptance of a blood flow of 200-250 ml/min has probably favored the results for untunneled catheters. Finally, culture results were not collected prospectively. As every exit-site culture and blood culture send from one of our hemodialysis patients to the department of microbiology was reviewed, it is not likely we missed infectious periods or introduced systemic errors favoring one of the catheter groups.

In conclusion, the present study shows that femoral, subclavian and jugular untunneled hemodialysis catheters are associated with a high rate of premature removals and infectious complications compared to TCC. According to our results, a TCC should be used whenever it can be foreseen that a hemodialysis catheter is needed for at least 14 days which is earlier than currently recommended by the NKF-DOQI. This indicates that almost no UC should be used in daily practice. However, when new strategies to reduce catheter-related complications like better designed untunneled jugular catheters and antimicrobial locking solutions [19 [20], are introduced in clinical practice, the outcome of UC may improve and new prospective randomized studies will be needed to estimate the time period untunneled catheters can be used safely.

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4 Prospective follow-up of a novel design hemodialysis catheter; lower infection rates and improved survival

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ABSTRACT

Background. Untunneled straight jugular catheters (USC) are uncomfortable for patients and can not be fixated well. This could be a reason for the high incidence of catheter-related complications.

Methods. We prospectively analysed the outcome of an untunneled precurved catheter (UPC), bending forward over the clavicle and fixated to the chest wall and compared it with the outcome of USC and tunneled cuffed catheters (TCC).

Results. The outcome of USC was documented over a 32 month period. Thereafter, we switched to an UPC. The same catheter care protocol was used and not changed over time. A total of 104 USC were inserted, 65 UPC and 64 TCC. Compared to USC, less UPC had to be removed for a complication (53 vs 15%; $p<0.001$) and less periods of catheter-related bacteraemia were observed in UPC compared to USC (0 vs 5.6 per 1,000 catheterdays; $p<0.01$ by log rank analysis). Removal for flow problems was similar. Compared to TCC, UPC were removed more often for flow problems (4.3 vs 1.0 per 1,000 cd; $p=0.024$), other outcomes and complication rates were similar. Complication rates for TCC inserted before and after the switch from USC to UPC were equal.

Conclusions. UPC have better patency rates and a lower risk for bacteraemia and exit-site infection compared to USC. Infection rates are similar to rates found in tunneled cuffed catheters.

INTRODUCTION

Temporary uncuffed haemodialysis catheters for vascular access are regularly used in haemodialysis practice. Today, the preferred site for a temporary catheter is the jugular vein. Uncuffed catheters are often left in place for a prolonged period of time despite the recommendation in the recently updated NKF-DOQI guidelines to use tunneled cuffed catheters (TCC) whenever it can be anticipated that a catheter will be needed for more than three weeks [1]. This is probably because inserting TCC requires more experience, prolonged procedure time and special skills of the operator.

In incident haemodialysis patients, 48% of catheters in the United States and 75% of catheters in Europe are untunneled and even in prevalent patients over a third of all catheters are untunneled [2]. It has been shown that catheter-related complications are higher for temporary untunneled jugular catheters compared to tunneled catheters [3;4]. The reasons for these increased rates are not clear. It is suggested that poor fixation could be important. Current models of untunneled straight jugular vein catheters (USC) are placed in the external or internal jugular vein pointing upward from the place of insertion. They are fixated cranial from the point of insertion and have either curved extensions (figure 1a) or are curved laterally. These catheters are uncomfortable for the patient and can easily dislocate. In addition, on connection to the haemodialysis machine, pulling lines can kink the catheter or cause laceration of the exit site, a known risk factor for infection [5;6].

Recently, a novel designed untunneled precurved temporary jugular catheter (UPC) model has become available (Duoflow®, Medcomp, Harleysville, USA). Inserted close to the upper border of the clavicle with the catheter bending over the clavicle and fixated to the chest wall, this catheter is more comfortable for patients (figure 1b). During haemodialysis treatment, movement of this catheter is minimal.

The primary aim of this study was to compare the patency and catheter-related complications of this precurved untunneled jugular catheter with untunneled straight catheters. We also related the results to the outcome of tunneled cuffed catheters during this study.

SUBJECTS AND METHODS

Patients and data collection

We analyzed all untunneled temporary jugular and tunneled cuffed haemodialysis catheters inserted in the jugular vein at the dialysis department of an academical teaching hospital over a 4 year period. On average, 60 haemodialysis patients are treated in our unit, 10% are patients with acute renal failure and 25% of patients depend on a catheter for vascular access. Data on all inserted catheters and catheter-related complications at follow up were entered prospectively in a computerized patient data system by the caring nephrologist and dialysis nursing team.
The decision on the type of catheter and place of insertion was left to the physician responsible for the patients care at time of insertion. In general, tunneled cuffed were more likely to be chosen whenever it could be foreseen that a catheter was needed for more than four to six weeks. When this could not be determined or the need for a catheter was expected to be shorter, a untunneled jugular catheter could be inserted. Reasons for catheter removal were entered in the database: elective removal, exit-site infection, catheter-related bacteraemia, flow problems, accidental removal or catheter fracture. Catheters were evaluated for type, place of insertion, time of insertion, duration of use and reason for removal. Femoral catheters were excluded. All cultures of blood and exit-sites taken from the patient during the period that a catheter was in place were collected from the computerized data system of the department of microbiology. Baseline patient characteristics and demographical data were collected at time of insertion. In addition, hospitalization for non catheter-related reasons at any time a catheter was in place and nasal staphylococcal aureus carrier was documented. Data on two catheters (both untunneled straight jugular catheters) were lost to follow-up shortly after insertion because of transferral of the patient to another dialysis center. These were excluded from the analysis.

Catheters, catheter care protocol and catheter outcome assessment

During the first 32 months of the study we used an untunneled dual lumen 11 Fr polyurethane catheter with curved extensions (Gamcath®, Hechingen, Germany (n=89)) and dual lumen 11.5 Fr polyurethane catheter with curved extensions (Mahurkar, Tyco, Mansfield, MA, USA (n=15)) for the jugular site (figure 1a). After this period, we switched to a novel design untunneled dual lumen polyurethane catheter (11.5 Fr; Duo-Flow® IJ, Medcomp, Harleysville, USA) (figure 1b). For TCC we used Neostar Circle-C® (cuffed silicon, Horizon Medical Products, Atlanta, GA, USA; n=48), PermCath® cuffed silicon (Tyco, Mansfield, MA, USA; n=5), Tesio twin-cath® cuffed silicon (n=3) and Ash-split® cuffed polyurethane (both Medcomp; n=8). All catheters were inserted under local anaesthesia and strict asepsis, and sutured to the skin. All untunneled and tunneled cuffed catheters were inserted after cannulation of the internal jugular vein close to (about one cm above) the clavicle, low in the sternocleidomastoid triangle in accordance to the puncture technique described by Rao et al [7]. A standard Seldinger guidewire procedure was used to introduce the catheter. Care was given to insert the catheter including the first half of the curve. After insertion, the exit site should point forward to downward. Ultrasound guidance was used whenever considered necessary.

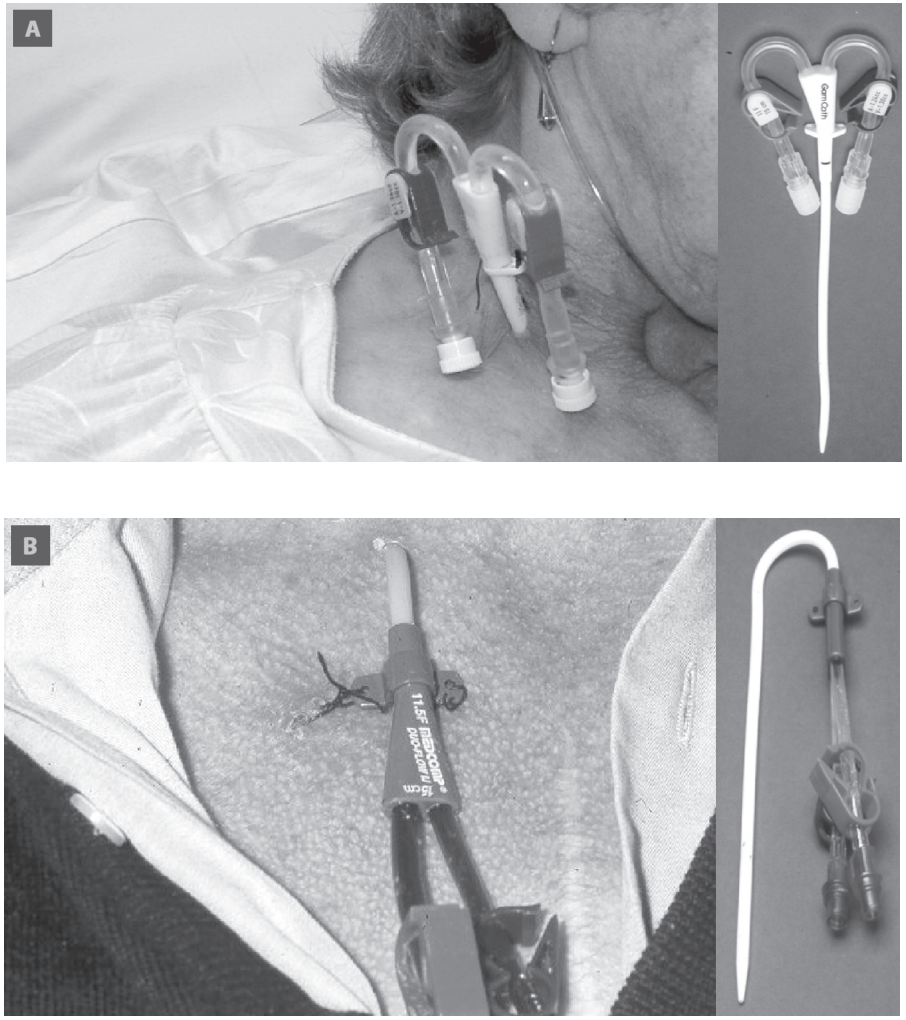

Figure 1. *Straight untunneled jugular catheter (a) and the novel precurved untunneled catheter (b).*

Catheter were inserted in the internal jugular vein about one cm above the clavicle (black line), low in the sternocleidomastoid triangle. A standard Seldinger guidewire procedure was used to introduce the catheter. Care was given to insert the catheter including the first half of the curve. After insertion, the exit site should point forward to downward. Catheters were only handled by experienced dialysis nurses or nephrology

staff, using sterile gloves and masks. The semi-occlusive dressings we used for exit-site care, were inspected at every dialysis session and changed at least once a week, the exit-site being cleansed with a povidone-iodine solution. Before removing the caps, the catheter hubs were disinfected with a chlorhexidine solution (2.5%). After dialysis treatment, catheters were locked with unfractionated heparin (5000 U/ml) with a volume equivalent to the internal volume of the lumen noted on the catheter. Catheters were used for haemodialysis exclusively. Catheter-related bacteraemia (CRB) was defined as fever (temperature > 38ºC) or cold chills not during a dialysis treatment with at least one positive blood culture and no other obvious cause of infection. In patients who developed signs of bacteraemia without symptoms of an alternative source other than the catheter, at least two blood cultures either from the catheter or from a peripheral vein were taken. Subsequently, antibiotics for suspected catheter related bacteraemia were given. When a catheter-related bacteraemia was established, the catheter was left in place in stable patients in whom fever disappeared after initiation of antibiotic treatment. In patients not improving within 48 hours or with recurrent bacteraemia within three weeks after stopping antibiotic treatment, the catheter was removed.
The policy was not different between untunneled catheters and tunneled cuffed catheters at our institution in the study period. In case of recurrent bacteraemia, only the first period was counted for the analysis.
Exit site infection was defined as the development of a purulent exudate or redness around the site not resulting from residual stitches. After culturing, antibiotic treatment was recommended for at least two weeks. In case of no improvement, the catheter had to be removed.

Flow problems

In accordance to national guidelines, the minimal acceptable Qb was 200 ml/min, the target was 250 ml/min. More important, the minimal acceptable dialysis dose was a urea Kt/V of at least 1.2 per treatment. When this could not be reached, the flow or dialysis duration could be increased. When a persistent inability to run a blood flow of more than 200 ml/min occurred despite positional changes of the patient and/or additional flushing, urokinase 10,000 IU/ml was installed in both pools with a volume equivalent to the internal volume of the lumen. After 15 minutes the urokinase was withdrawn. If a blood flow of more then 200 ml/min was not achieved after this procedure, 100,000-250,000 IU of urokinase could be infused in three hours during dialysis according to the protocol of Twardowski [8]. When this was not successful, the catheter was removed or exchanged.

Statistical analysis

Statistical analysis was performed with SPSS software 11.2 (SPSS Inc., Chicago, Ill, USA). Non parametric tests for two (Mann-Whitney U test) and multiple continuous variables (Kruskal-Wallis test) were used. For comparing binary and categorical variables Chi-square and Fisher's exact tests were applied where appropriate. ANOVA was used to compare age and time on dialysis between multiple groups. Kaplan-Meier survival curves were constructed to analyze the patency rates and infectious complications.

Functional catheters at the end of the observation time and catheters removed because they were not needed anymore were analyzed as censored values. The log rank test was used to compare groups and identify individual risk factors associated with a premature removal or catheter-related infection. At an individual two-sided P value of < 0.1, the factor was included to fit a Cox-regression model.
We used a forward stepwise conditional technique to identify the factors independently associated with catheter failure and infection. Differences were considered statistically significant for *p* less than 0.05.

Table 1. Base line characteristics of the patients and catheters

Characteristic	Untunneled catheters		Tunneled cuffed catheters
	Straight (n=104)	Precurved (n=65)	(n=64)
Catheter days (no.)	3209	2101	9124
Time left in place (mean (range))			
All catheters	31 (2-162)	35 (5-232)	142 (7-604)
Uncomplicated catheters	30 (2-132)	32 (5-232)	146 (13-568)
More than three months (%)	6	3	52
Right sided insertion (%)	84	91	88
Age (mean ± SD)	61.0 ± 13.8	58.7 ± 16.4	58.7 ± 14.7
Race			
Caucasian (%)	71	72	72
Black (%)	18	20	19
Other (%)	11	8	9
Male sex (%)	66	59	53
Yr of dialysis (mean ± SD)	1.2 ± 2.1*	1.3 ± 2.2	2.1 ± 2.5*
Cause of end stage renal disease			
Diabetes (%)	24*	11*	27*
Renovascular (%)	20	11	11
Polycystics disease (%)	8	11	14
Glomerulonephritis (%)	13	22	17
HIV (%)	1	2	1
Other (%)	24	28	24
Unknown (%)	10	15	6
Acute renal failure (%)	38**	29**	9**
Diabetes mellitus (%)	27	19	30
Cardiovascular disease (%)			
Coumarin use (%)	8 ‡	17	23 ‡
Immune suppression (%)	14	17	9
Malignancy (%)	9	3	5
Staphylococcus Aureus carrier (%)	48	45	44

Abbreviations: SD, standard deviation
* P<0.05
** P<0.01
‡ P<0.01

RESULTS

A total of 233 haemodialysis catheters (14,434 catheter days) were included in the final analysis. There were 104 untunneled straight jugular catheters (USC) inserted, 65 untunneled precurved jugular catheters (UPC) and 64 tunneled cuffed catheters (TCC). Patient and catheter characteristics are given in table 1.
Of patients who had a TCC inserted, 91% was on chronic haemodialysis treatment in contrast to patients with an USC (62%, p<0.01) and to the group with an UPC (71%, p<0.01). Patients with an UPC had higher hospitalization rates for other than catheter-related reasons compared to TCC (54% vs 34%, p<0.05). Also, patients with UPC were less likely to have diabetes diagnosed as primary cause for end stage renal disease compared to TCC (p<0.05). Furthermore, patients with a TCC were on coumarin treatment more often (8 vs 23%, p<0.01). Other differences in patient characteristics were not statistically significant. Patient and catheter characteristics of TCC inserted before (n=31) and after (n=33) the switch from USC to UPC, were similar. Most catheters were right sided (87%). Since there was no significant difference in outcome between catheters inserted in the right or left jugular vein, they were not separated in the definite analysis.

Table 2a. Summary of premature removals and catheter-related complications

	Untunneled catheters		**Tunneled cuffed catheters**
	Straight n (=104)	Precurved n (=65)	n (=64)
Variable	no. of events (%)		
Premature removal			
for any complication	55 (53)	10 (15)	22 (34)
no. per 1000 cath. days	17.1	4.3	2.4
For any infection	37 (36)	0	9 (14)
no. per 1000 cath. days	11.5	0	1.0
For flow problems	16 (15)	9 (14)	9 (14)
no. per 1000 cath. days	5.0	4.3	1.0
For fracture / accidental / removal / other	2 (2)	1 (2)	0.4
Catheter-rel. bacteremia	18 (17)	0	16 (25)
no. per 1000 cath. days	5.6	0	1.8
Exit-site infection	32 (31)	0	14 (22)
no. per 1000 cath. days	10.0	0	1.5

UPC denotes untunneled precurved catheters, USC denotes untunneled straight catheters and TCC denotes tunneled cuffed catheters. Comparison between UPC and TCC was corrected for years on dialysis and acute renal failure.

Table 2b. Summary of premature removals and catheter-related complications

	Cox-regression analysis of outcome and complications	
	UPC vs USC	UPC vs TCC
Variable	relative risk (95 percent confidence interval)	
Premature removal		
for any complication	0.22 (0.11-0.44); p<0.0001	1.48 (0.92-2.37); p=0.11
no. per 1000 cath. days		
For any infection	0.02 (0.01-0.33); p=0.006	0.15 (0.01-5.80); p=0.08
no. per 1000 cath. days		
For flow problems		
no. per 1000 cath. days		
For fracture / accidental / removal / other		
Catheter-rel. bacteremia	0.02 (0.01-0.97); p=0.048	0.16 (0.01-3.13); p=0.23
no. per 1000 cath. days		
Exit-site infection	0.04 (0.01-0.29); p=0.002	0.36 (0.13-1.01); p=0.053
no. per 1000 cath. days		

UPC denotes untunneled precurved catheters, USC denotes untunneled straight catheters and TCC denotes tunneled cuffed catheters. Comparison between UPC and TCC was corrected for years on dialysis and acute renal failure.

CATHETER OUTCOMES

Of 65 UPC inserted, 55 (85%) could be used until they were not needed anymore compared to only 49 (47%) of 104 USC (relative risk for premature removal 0.22; 95% CI 0.11-0.44; p<0.001). The rate of premature removal was reduced from 17.1 to 4.3 per 1,000 catheter days after switching from USC to UPC. Although not statistically different, premature removal rates were higher with UPC compared to TCC (2.4 vs 4.8 per 1,000 catheter days; p=0.11). Characteristics of premature removals are shown in table 2.There was a reduction of 11.5 to 0 removals for catheter-related infections per 1,000 catheter days after switching from USC to UPC (p<0.01). However, removals for flow problems were similar (5.0 vs 4.3 per 1,000 catheter days; p=0.27). TCC were characterized by less removals for infection (1.0 per 1,000 catheter days; p<0.001) compared to USC and less removals for flow problems compared to both untunneled catheter groups (1.0 per 1,000 catheter days; p<0.05) Log rank analysis of survival curves showed better rates for UPC compared to the USC group (p<0.0001) and similar rates compared to TCC (p=0.24, corrected for years on dialysis and acute renal failure) (figure 2). The risk for premature removal of TCC inserted before and after the switch from USC to UPC was not statistically different (relative risk 1.33; 95% CI 0.55-3.26; p=0.52).

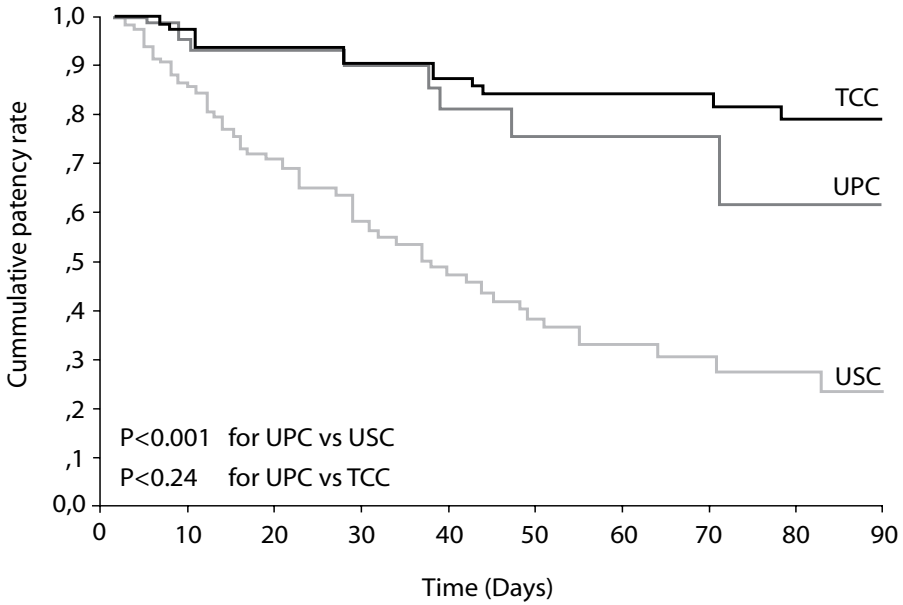

Figure 2. *Kaplan-Meier curves of cumulative catheter patency for untunneled precurved jugular catheters (UPC) (——) compared to untunneled straight jugular catheters (USC) (——) (p<0.001 by log rank statistics) and tunneled cuffed catheters (TCC) (——) (p=0.24 by log rank statistics, , corrected for years on dialysis and acute renal failure). Tick marks indicate censored catheters.*

INFECTIOUS COMPLICATIONS

In patients with an UPC inserted, no episodes of catheter-related bacteraemia (CRB) occurred. One catheter was instantly removed in an immune compromised patient who presented with fever. However, an alternative diagnosis was made during follow up. There was a reduction of CRB episodes after switching from USC to UPC (5.6 to 0 per 1,000 catheter days; p<0.001 by log rank testing) (figure 3a). CRB rates of UPC were also lower compared to TCC (0 vs 1.8 per 1,000 catheter days; p=0.04 by log rank testing) (figure 3b).

Exit-site infection rates were also lower after introduction of UPC compared to both USC and TCC. Differences in CRB and exit-site infection rates within the catheter groups are presented in table 2. The risk for CRB and exit-site infection in the TCC group during both periods was equal (relative risk 1.01; 95% CI 0.47-2.17; p=0.97).

In 42% of cases cultures yielded gram-positive micro organisms, predominantly Staphylococcus aureus or Staphylococcus epidermidis, in 34% it concerned gram-negative micro organisms. The remaining cultures revealed multiple micro organisms or yeasts.

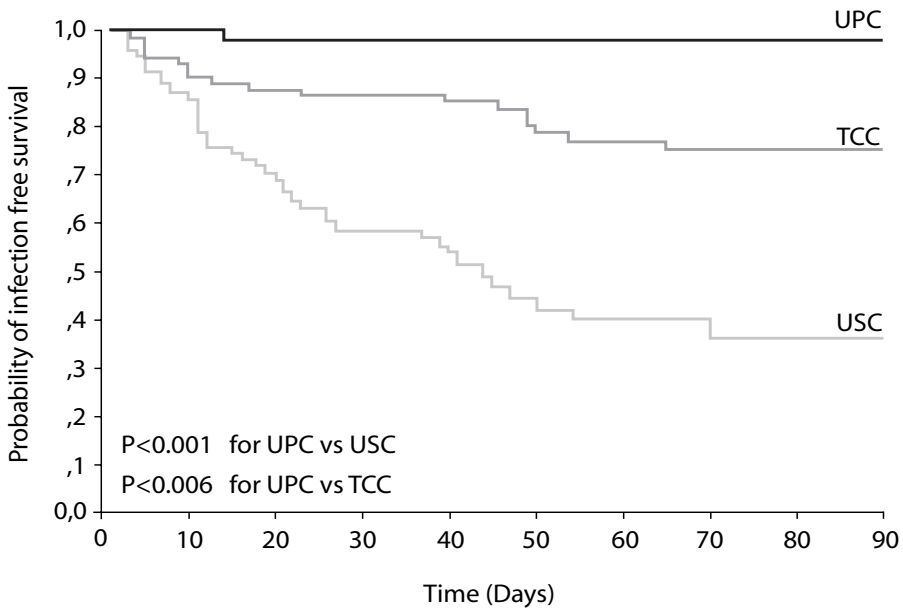

Figure 3a. *Kaplan-Meier curves of probability of infection free survival for untunneled pre-curved jugular catheters (UPC) (——) compared to untunneled straight jugular catheters (USC) (——) (p<0.001 by log rank statistics) and tunneled cuffed catheters (TCC) (——) (p=0.006 by log rank statistics, corrected for years on dialysis and acute renal failure). Tick marks indicate censored catheters.*

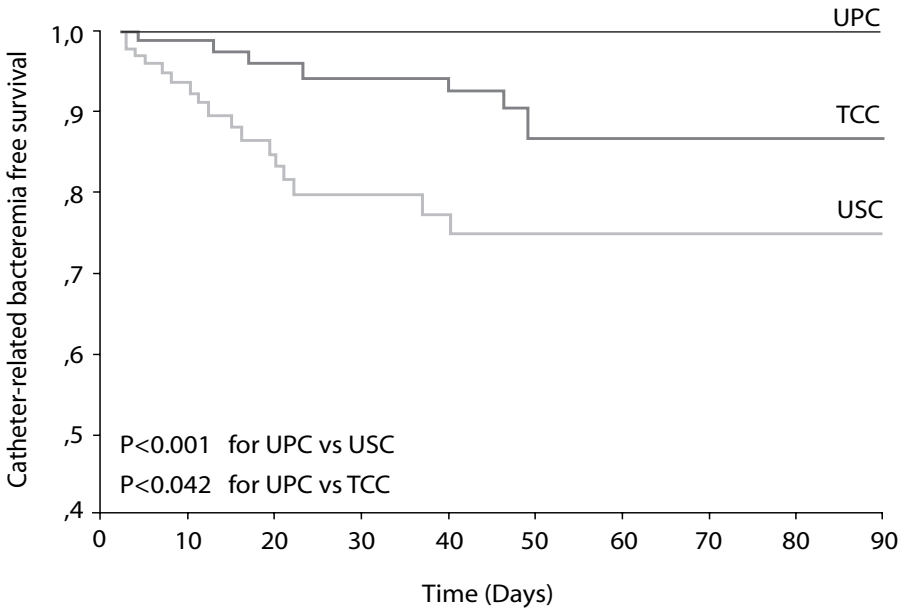

Figure 3b. *Kaplan-Meier curves of probability of catheter-related bacteremia free survival for untunneled precurved jugular catheters (UPC) (——) compared to untunneled straight jugular catheters (USC) (——) (p<0.001 by log rank statistics) and tunneled cuffed catheters (TCC) (——) (p=0.042 by log rank statistics, corrected for years on dialysis and acute renal failure). Tick marks indicate censored catheters.*

DISCUSSION

Our study demonstrates that a novel design forward bended precurved haemodialysis catheter inserted in the low jugular site has a better survival and lower risk for infection compared to a straight jugular catheter.

There are some possible explanations for these findings. In the present study the reduction of exit-site infections for UPC (0 per 1,000 catheter days) compared to USC (10 per 1,000 catheter days) was remarkable and this probably partially explained the reduction in catheter-related bacteraemia. An important problem of USC is that an adequate fixation is difficult and that they are uncomfortable for the patient because neck and head movements are limited. Inadequate fixation and discomfort leads to more manipulation, sliding of the catheter through its port and can easily give laceration and secondary infection of the exit-site. These are well known risk factors for subsequent catheter-related bacteraemia [9;10]. In addition, straight jugular catheters have an upward directed exit site. In peritoneal dialysis catheters, this is a well established risk factor for exit-site infections and peritonitis [5;6]. Probably, with an upward directed

exit-site, adequate drainage of debris is prohibited and colonization of the catheter exit-site promoted which can cause local infection and subsequent systemic infection. Therefore, in peritoneal dialysis catheter management a downward directed exit-site is recommended.

Exit-site colonization can also lead to catheter hub colonization and subsequent bacteraemia. This could also be an explanation for the differences found in this study, but as regular cultures of the hub were not performed, this remains speculative.

The same reduction of colonization and infections in exit-sites that permit an adequate drainage could also be the reason that in recent studies untunneled temporary straight jugular catheter had higher rates of infectious complications compared to untunneled subclavian catheters [3;4]. The precurved untunneled catheter used in this study has the advantage of a forward to downward directed exit-site that makes adequate drainage of debris possible. The improved fixation properties and exit-site direction are likely the most important explanation for the reduction of infection rates in untunneled precurved catheters compared to untunneled straight catheters. As overall outcome between UPC and TCC was not different, UPC can be an attractive alternative for the time period studied. Possibly infectious data might have differed slightly because the mean time UPC were left in place was shorter than for TCC and infectious rates can rise over time.

There are limitations to our study. The prospective sequential cohort analysis of the USC and UPC respectively, instead of a randomized design, could have led to bias due to unnoticed differences in time, not accounted for by baseline characteristics. Furthermore, the propensity for inserting a TCC instead of an uncuffed catheter might have changed over time. However, since outcome in TCC in the two time periods did not change, this probably did not influence the results. Also, the analysis between the uncuffed catheters on the one hand and the TCC on the other might be biased due to lack of randomisation and differences in indication.

There were observed differences in baseline characteristics, like the presence of diabetes and the incidence of acute renal failure. However, in contrast to many other studies, we corrected for these differences in the outcome analysis.

Previous studies in tunnelled catheters have suggested that catheter-related complications, especially infections, are constant over time or tend to decrease [3;11;12]. Furthermore, as shown in the Choice study, few patients will need a catheter for more than three months [13]. Considering catheter-related infections as major drawback for catheter use, our results show that an untunneled precurved catheter for the period of three months could be a safe option, more convenient for the patient and physician during insertion and probably cost-saving. Compared to TCC, these catheters are six to eightfold less expensive. This is in contrast with the NKF-DOQI guidelines which state that a tunnelized catheter should be used whenever it can be foreseen that a catheter is needed for more than 2 to 4 weeks [1]. However, these guidelines are predominantly expert based or supported by studies with untunneled straight catheters including our own [3;4].

Compared to tunneled cuffed catheters, more untunneled precurved catheters had to be removed for flow problems. This was probably caused by the fact that

tunnelled cuffed catheters have a 2–3 Fr larger diameter and the flow resistance is related proportional to the diameter of a catheter to the fourth power. Therefore, it is clear that flow characteristics are better in tunneled cuffed catheters and that there is more flow reserve in the case of partial obstruction. Probably, the function of untunneled precurved catheters can be improved by increasing its diameter and tip construction [14].

Another confounding factor in catheter studies influencing the outcome of catheters is the catheter care protocol. It has been shown in randomized studies that the risk for CRB can be reduced with a thorough protocol [15;16]. In our study, catheter care protocol was not changed over the entire observation period and the incidence of catheter-related infections of tunneled cuffed catheters in the time periods untunneled straight catheters (first period) or untunneled precurved catheters (second period) were used, were not statistically different making a time bias and differences in catheter care as explanation for our findings unlikely.

In conclusion, our study demonstrates that in addition to improved patient comfort, an untunneled precurved jugular haemodialysis catheter has better patency rates and a lower risk for infection compared to a straight jugular catheter with curved extensions. The risk for bacteraemia and exit-site infection is comparable to tunneled cuffed catheters for the first three months these catheters are left in place.

This novel design precurved catheter placed in the lower jugular position should be preferred as untunneled jugular catheter model over straight models with curved extensions and can be used safely when it can be foreseen that a catheter is needed for up to three months. Our results make a prospective randomized trial comparing TCC to UPC with wider inner diameter an important issue for the future.

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5a Clinical implications of hemodialysis catheter construction

A Scanning Electron Microscopy Analysis of a Spontaneous Hemodialysis Catheter Fracture.

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Am J Kid Dis 2001;38:858-861

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ABSTRACT

Central venous catheters have become increasingly important in hemodialysis treatment. With their increased use catheter-related problems will be seen more frequently and more rare complications may be observed. We describe the first case of an asymptomatic spontaneous breakdown of a tunneled cuffed silicone catheter used for long-term hemodialysis treatment. This was discovered on removal of the catheter, leaving behind a catheter fragment in the left lower pulmonary lobe. An extensive scanning electron microscopy study showed accumulation of lumps of non-silicone material at the place of the fracture leading to severe disruption of the original cross-linked elastomer structure. Utilizing energy dispersive X-ray spectral analysis, that reveals all elements with atomic number of eleven and up in a material, we found the lumps to be aggregates of bariumsulphate particles used to visualize the catheter on fluoroscopy. We suggest that the use of too small or too much bariumsulphate particles has led to high viscosity of the raw silicone before polymerization, causing improper mixing of bariumsulphate particles in the silicone matrix. This resulted in insufficient removal of admixed airbubbles and unequal dispersion of bariumsulphate with the potential for weak spots after extrusion of the silicone into its definitive shape. With the increasing use of hemodialysis catheters for prolonged times, catheter-related complications, related to materials or manufacturing errors can be expected to occur more often.

INTRODUCTION

Hemodialysis treatment requires reliable access to the circulation. An arteriovenous (AV) fistula or an AV-graft is recommended for chronic treatment.[1] In a recent survey[3] however, only 34% of hemodialysis patients had a functional permanent AV access at the start of treatment. At present tunneled cuffed hemodialysis catheters have come to play an increasingly important role in the delivery of hemodialysis treatment.[2] Currently, approximately 19% of all hemodialysis patients in the United States have a catheter as access for chronic hemodialysis treatment. The two major complications of hemodialysis catheters are thrombosis and catheter-related infections. With its growing use it can be anticipated that material and manufacturing problems will be observed increasingly. We report a spontaneous fracture of a silicone hemodialysis catheter leaving behind a fragment in the lung. Scanning electron microscopy revealed the cause of the fracture.

CASE

A 50-year old woman was referred to our hemodialysis department in August 1999 because of end stage renal failure due to diabetic nephropathy. Because of late referral an AV-fistula had not been formed in the patient. Therefore, a tunneled double-lumen silicone hemodialysis catheter (AC 230C, Neostar Circle C, 13,5 F, length 23 cm, Horizon Medical Products, Atlanta, GA) was placed in the right jugular vein under local anesthesia. Subcutaneous tunneling was performed according to the instructions provided by the manufacturer. The procedure was uneventful and a chest X-ray (anterior-posterior and lateral view) after the procedure disclosed an intact catheter with the tip in the right atrium. The catheter was used for hemodialysis treatment two times a week aiming at a bloodflow of 250 ml/min and low molecular weight heparin for anticoagulation. At the end of each dialysis session unfractionated heparin (5000 IU/ml) was instilled for locking. After nine months the catheter could be removed because a functioning AV-graft was available. Monthly measured Kt/V and urea-reduction rates had remained stable over the period of insertion and venous return pressures had not exceeded 170 mmHg. Three periods of intraluminal catheter thrombosis had been successfully treated with a fifteen-minute installation of urokinase (10.000 U/ml). Catheter stripping or intraluminal manipulations with guidewires or brushes had not been performed and no infections were observed. Removal of the catheter took place without any difficulties. No excessive pulling was needed. The procedure was uneventful and the patient mentioned no complaints. After removal, the catheter-tip appeared to be broken of (Figure 1).

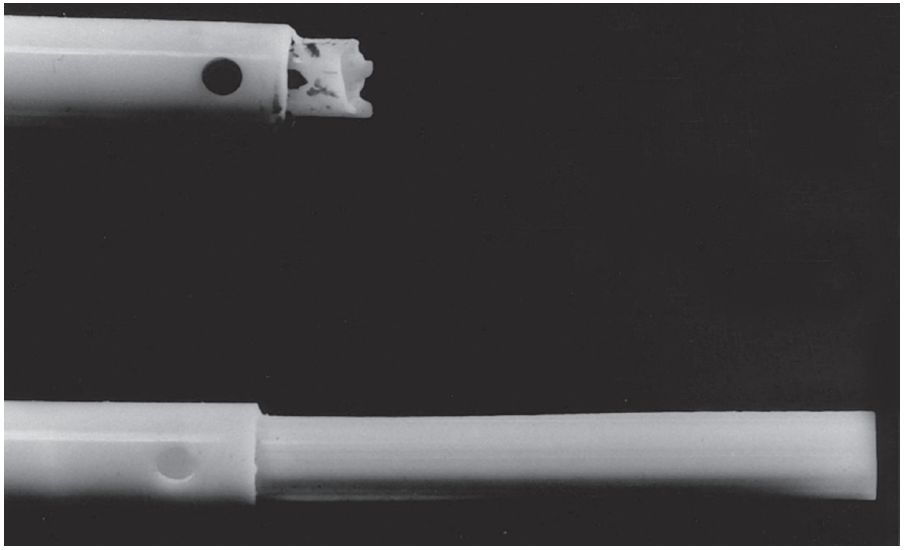

Figure 1. *Tip of the broken and an intact catheter.*

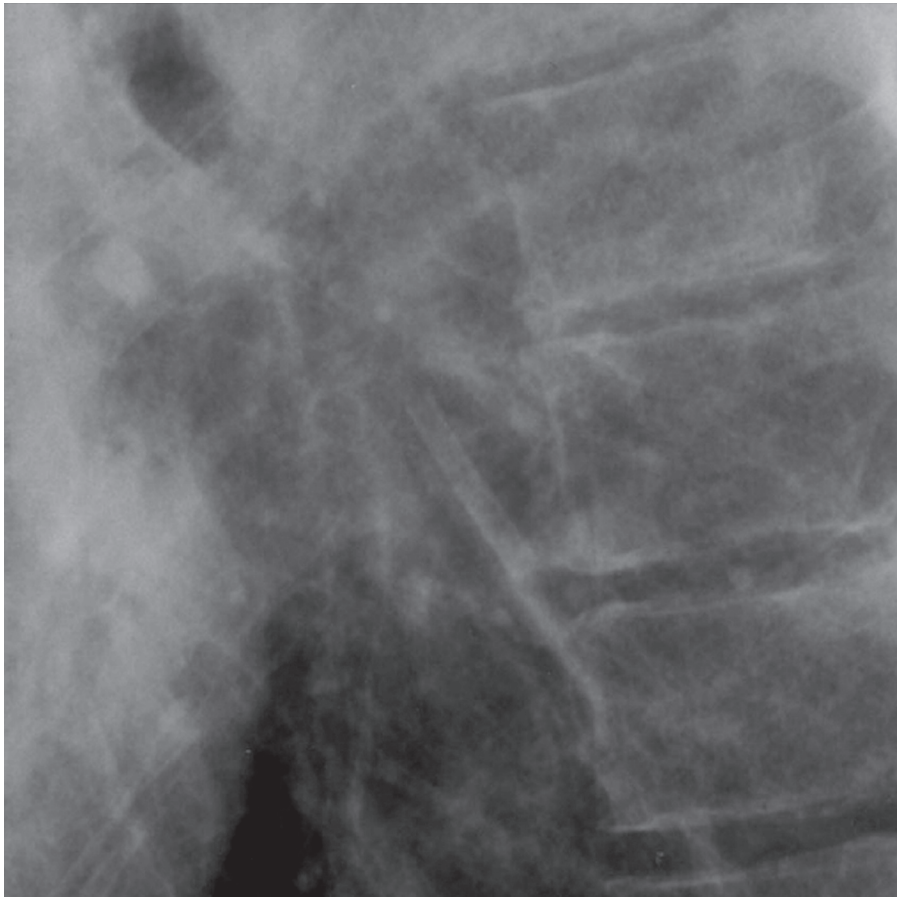

Figure 2. *Fragment of the catheter in the left lower pulmonary lobe. On the left side the posterior border of the heart is visible.*

A chest X-ray showed the tip of the catheter in the lower lobe of the left lung (Figure 2). No clinical or radiographical signs of inflammation or pulmonary embolism have developed until now.
Scanning electron microscopy of the catheter showed multiple spots with aggregates of particles causing irregular cavities in the solid structure of the silicone rubber (Figure 3f). At the place of the fracture these aggregates had formed a large lump. The original cross-linked elastomer structure of the silicone was not recognizable anymore and the tear that started the rupture was visible (Figure 3a,b).
Energy dispersive X-ray spectral analysis showed the particles to be bariumsulphate grains used to visualize the catheter on X-ray.

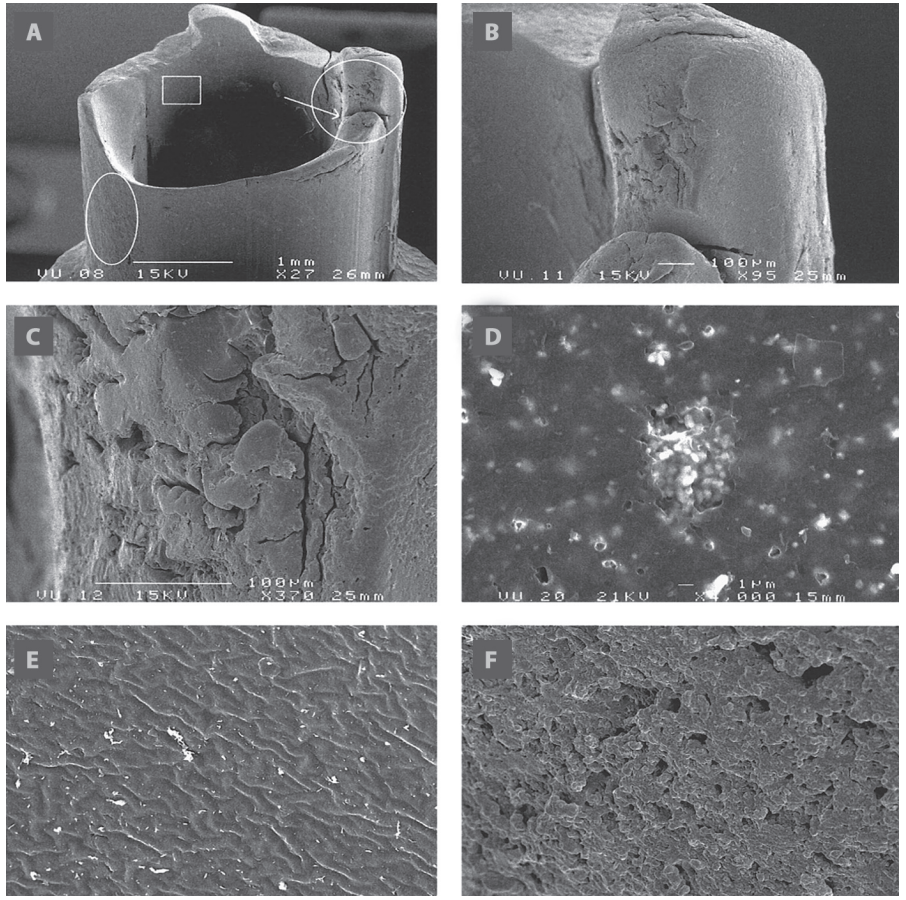

Figure 3. *Scanning electron microscopy analysis.*
A. *Overview of the fracture. In the circle the abnormal surface and structure is visible including a tear (arrow) where the fracture started. The oval shows a part of the catheter with a very irregular surface. In the rectangle the normal surface structure is apparent.*
B. *Detail from the white circle in A.*
C. *Further magnification of B, showing a lumpy texture full of voids lacking internal cohesion and beginning ruptures.*
D. *A bariumsulphate lump with backscatter technic clearly shows entrapped air, causing a weakness zone in the silicone matrix.*
E. *Normal smooth inner surface of the catheter.*
F. *Porous surface in the rupture zone (C) showing aggregates of bariumsulphate with admixed air without the normal continuous phase of cross-linked elastomer recognizable.*

DISCUSSION

To our knowledge this is the first report of a ruptured hemodialysis catheter leaving behind an intravascular fragment. Spontaneous catheter fractures with fragments remaining intravascular have been reported mainly in patients with not used for hemodialysis.[4-5] The exact incidence of catheter rupture is unknown. Recently Biffi *et al* reported an incidence of 0,68% in 1320 subclavian port placements.[6] Mainly such fragmentation concerned catheters inserted in the subclavian vein with the fracture at the place of passage under the clavicle, the so called "pinch-off" syndrome.[7] Catheter fragments may cause severe complications like cardiac arrest, vascular perforation and pulmonary embolism.[8] Recently two cases of spontaneous breakdown of a hemodialysis catheter have been reported one causing extensive recirculation[9], the other leakage[10] but no free fragment developed. In both cases the exact cause was not unraveled.

In our case it is not likely that the rupture was caused by accidental damage to the catheter at insertion or removal. On insertion no problems were encountered and no manipulations with the tip of the catheter had been performed. The initial chest X-ray showed an intact catheter with the tip in a normal position. During the period of insertion no guidewires or brushes had been used. Urokinase, installed three times, is a proteolytic enzyme that is not known to degradate polymer structures. Therefore, it seems unlikely that its administration affected the structure of the silicone.

In the present case the most likely cause is an error in the manufacturing process. By extensive scanning electron microscopy and energy dispersive X-ray spectral analysis (that reveals all elements with atomic numbers of eleven and up in a material) we could demonstrate that the bariumsulphate particles, used to visualize a catheter on fluoroscopy, were not properly mixed in the silicone rubber matrix.

Ideally all powder particles should be separately dispersed in the raw silicone material before polymerization to preserve tensile strength as much as possible.[11] In the studied catheter, however, bariumsulphate particles formed aggregates of variable size. The larger bariumsulphate powder lumps have trapped airbubbles that formed elongated cavities on extrusion. These cavities are clearly visible, both as irregular disruption of the surface (Figure 3b) and as voids within the silicone matrix (Figure 3f). The presence of these powder lumps points to insufficient mixing, probably caused by the particle size of the bariumsulphate powder. For a given amount of powder, the size of bariumsulphate particles defines the number. The bigger the number is, the greater the total surface of the powder resulting in a higher viscosity of the silicone paste after mixing. This hampers removal of admixed airbubbles from the suspension before extrusion to its final shape. Because the amount of bariumsulphate is defined by the grade of X-ray contrast needed for fluoroscopy, the only way to lower the total surface of the powder and lower the viscosity of the suspension is using a coarser particle size.

Biodegradation and breakdown of silicone caused by chronic inflammation in a biofilm and production of strong oxidants by bacteria have been described.[12] Neu *et al* showed that microorganisms can grow into silicone material, causing deterioration of the material.[13] However, on scanning electron microscopy we could not detect microorganisms in the rupture, nor in the cavities with bariumsulphate particles.

Fortunately, until now the patient experiences no complaints of the fragment in the left lung. Percutaneous transvenous snare technique is the therapy of choice to retrieve dislocated fragments. However, due to the peripheral position of the fragment in our patient the only possible way to remove it would be a segmental resection of the pulmonary lobe. Since catheter fragments have been left in place for a long time without complications[4] and our patient has no complaints, we decided to leave the fragment in place.

In the aforementioned two reports of hemodialysis catheter breakdown a clear reason was not found[9-10], suggesting the possibility of a catheter construction problem also. However, electron microscopy had not been performed. With the increasing use of hemodialysis catheters for prolonged times, catheter-related complications, related to materials or manufacturing errors can be expected to occur more often.

We would like to acknowledge W.J. Lustenhouwer, Microanalytical Laboratory, and Faculty of earth sciences, for the interpretation of the scanning electron microscopy analysis.

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5b Clinical implications of hemodialysis catheter construction

Do catheter side holes provide better blood flows?

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ABSTRACT

Four catheters (Ash Split Cath, Tesio, Duo-Split and DuoFlow; Medcomp, Harleysville, PA, U.S.A.) were tested in a temperature-controlled in vitro setup filled with 50% aqueous glycerine solution, to determine hydraulic resistance at different flow rates.
All these catheters have side holes; hydraulic resistance was determined with these holes open or closed. Due to extra pressure losses near the catheter tip, the pressure-flow relationship deviates from Poiseuillian theory and is generally quadratic in nature.
An equivalent diameter was derived from the data. This equivalent diameter can be used to evaluate performance using a single number.
Permanent catheters can easily deliver 300 ml/min under optimal circumstances, but acute catheters are, In practice, limited to 200 ml/min and even somewhat less in the coaxial Duo-Flow type. Permanent catheters have larger equivalent internal diameters (1.8 vs. 1.45 mm). Covering the side holes does not influence the hydraulic resistance to a great degree, except in the arterial limb of acute catheters. These results indicate that, especially in acute catheters, obstruction of the side holes or fibrinsleeve/thrombus formation over the inlet holes may severely impact the available blood flow rate during dialysis. On the other hand, side holes in permanent catheters or venous limbs seem to be superfluous for performance reasons.

INTRODUCTION

Central venous catheters have earned their place among the different methods of vascular access for hemodialysis (HD). Apart from their use in situations where immediate access to the blood is required [1, 2], catheters are increasingly employed for the delivery of dialysis to patients with end-stage renal disease [3]. This has increased interest in the performance of catheters to provide adequate dialysis and, consequently guidelines have been set forth [4]. The National Kidney Foundation-Dialysis Outcomes Quality Initiative (NKF-DOQI) guidelines [5] set the lower limit to 300 ml/min for extracorporeal blood flow to be able to treat the patient without need for lengthening the duration of the procedure. Yet, due to frequent infection and thrombosis, catheters show the lowest patency rate of all current methods of HD access [6]. Thrombus formation in most cases is easily remedied by means of a thrombolytic agent [7,8]. However, infection is a more severe problem, the rate of which depends not only on the catheter handling [9,10] in the dialysis unit and by the patient, but also on the biocompatibility of the catheter material [11-13]. The same accounts for thrombogenesis on the inner or outer surface of the catheter [14], although local hemodynamics also play a role in this process [15].
Catheters serve a simple purpose: to guide the venous blood towards the HD machine and bring it back into the venous system in a safe ane reliable way. Therefore, it is remarkable that the geometrical designs of their blood conduits and tips differ substantially [16,17]. Different catheters are equipped with a number of side-holes of various sizes and positions on the catheter wall. The common belief is that multiple side holes are needed to provide backup in case the apical or some of the side holes become obstructed by venous wall suction or a fibrin sleeve [14,17]. However, it has never been thoroughly investigated whether these side holes are able to allow the required blood flow rate. In addition, the absence of any adverse effects through the presence of these holes has not been well studied. Schwarzmann and Sefrin [18] concluded that a catheter with multiple holes does not show any advantage as far as thrombogenicity is concerned. Twardowski and Moore [19] suggested that side-holes predispose to the formation of thrombi, as they observed, using scanning electron microscopy, rough edges of holes and clots firmly anchored to the holes of removed catheters.
The goal of the present study was to measure the performance of dual-lumen catheters in an *in vitro* setup by studying their pressure-flow relationships. We also investigated the influence of closing off some of the side-holes to see if that would impact the performance.

MATERIALS AND METHODS

To obtain reproducible pressure-flow relationships under standardized conditions, a dedicated in vitro measurement setup was built. The setup consisted of two reservoirs connected by two recirculation loops (Fig.1). The upper reservoir's fluid level was kept constant by continuous recirculation from the bottom reservoir and an overflow tube. This ensured that a constant pressure of about 2 mmHg is present at the catheter tip. The second recirculation loop was made up partly of the catheter circuit; the other part was shared with the first recirculation loop. The catheter circuit either ran from the lower

reservoir and through a dialysis roller pump to the venous lumen of the catheter, or it starts at the upper reservoir and pased through the arterial lumen of the catheter and the dialysis roller pump to the lower reservoir. The circuit is filled with a 50/50% aqueous solution of water and glycerine and kept at a constant temperature of 30°C using a controlled coil heater. This ensured that the viscosity remained constant at 4.8 mPa (or cP), slightly elevated to actual blood viscosity at normal hematocrits (40-45%) for reasons explained later. Dialysis patients have a similar blood viscosity due to elevated plasma viscosity, increased red blood cell (RBC) aggregation, and decreased RBC deformability [20].

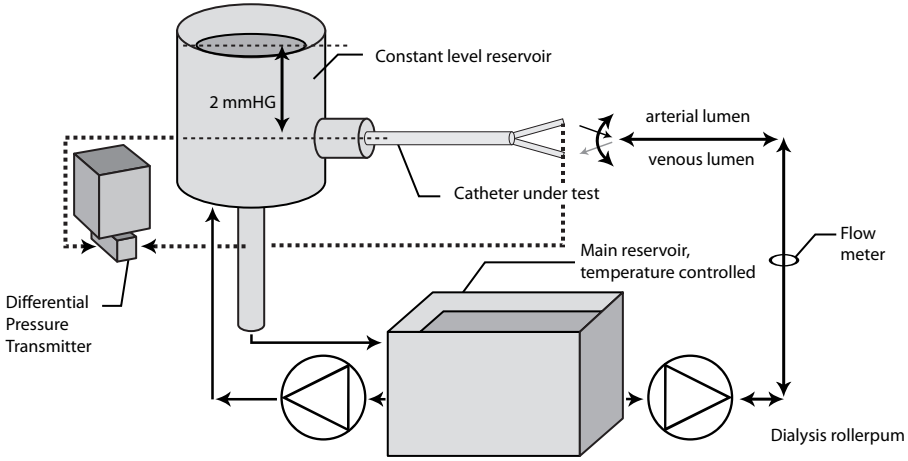

Figure 1. *Overview of the measurement set-up. The catheter tip is in the constant level reservoir. The dialysis pump either pumps the fluid into the venous lumen or draws it from the arterial lumen.*

Flow rate was determined by an ultrasound transit-time clamp-on flow meter (Transonic, Ithaca, NY, U.S.A.), 10-point calibrated for the glycerine solution by a gravimetric method over the total measurement range of 0 - 500 ml/minute.
The pressure drop over the catheter was measured with a differential pressure transmitter (Fuji electric, Erlangen, Germany) set to full scale (300 mmHg or 40 kPa).
The pressure inputs of the transmitter were connected to the Luer lock of the lumen and to the constant level reservoir for reference. Both electronic devices were connected to a computer data-acquisition system (National Instruments, Zaventem, Belgium) for data processing.
The roller pump speed was gradually adjusted to increase the flow rate through the catheter. To determine a single data point, flow rate and pressures were recorded during a finite time, with a sampling rate of 200/second. Due to roller pump operation, these curves exhibit a periodical pattern. To level out the pulsatility of the roller pump and the eventual unequal occlusivity of the two rollers, mean levels of flow rates and

pressure differences were obtained by taking the average of an even number of periods. All averaged points were used to fit a parabolic equation through the origin [Eq. (1)], stating the pressure drop (ΔP)-flow rate (Q) relationship of the catheter lumen.
The parabolic equation was obtained by polynomial regression (Sigmaplot, SPSS Inc., Erkrath, Germany);

$$\Delta P = aQ + bQ^2. \qquad (1)$$

Care was taken to ensure both parameters (a and b) of the fit-equation were statistically significant ($p<0.05$) to describe the data set. Performance can also be characterized by the hydraulic resistance (R), which is not constant as the Poiseuille equation suggests, but a linear function of the flow rate [Eq. (2)]:

$$R = \Delta P/Q = a + bQ. \qquad (2)$$

To compare the different catheters in a standard manner, the concept of equivalent diameter (D_e) was used. The D_e is determined from the effective diameter (D_{eff}). The D_{eff} is defined as the internal diameter that a circular tube with the same length (L) as the catheter lumen should have, to exhibit the same pressure drop as the catheter under study at a particular flow rate. For laminar flow it is derived from the well-known Poiseuille equation and is defined by Eq. (3):

$$D_{eff} = (128\mu LQ/\pi\Delta P)^{1/4}. \qquad (3)$$

D_{eff} should be independent on the fluid's dynamic viscosity (μ), as its effect is cancelled by the flow/pressure drop ratio. However, D_{eff} depends on the flow rate because of special pressure losses in the catheter that are not linearly proportional to the flow rate.
For a As a reasonable approximation, it can be assumed that D_{eff} varies quadratically with the Reynolds number (Re). Therefore, the actual D_e is obtained in an iterative fashion as the D_{eff} at Re=1000 on the polynomial regression line that is fitted through all Deff in the laminar range. Reynolds number (Re) is defined as:

$$Re = 4\rho Q/\pi D e\mu \qquad (4)$$

Where D_{eff} is the density of the glycerin solution (1128 kg/m^3). Since the most correct results are obtained at equal Re numbers for blood and test fluid [21], and since the ratio of the viscosity to density determines the Re number, a slightly elevated viscosity was used for the test fluid to correct for the higher density of the glycerin mixture with respect to whole blood. The higher the pressure drop is at Re=1000, the lower the D_{eff} becomes. At Re=1000, a flow rate of about 350 ml/minute was attained in this set-up for the permanent catheters, and about 250 ml/minute for the acute catheters.
In this study, four catheters with side holes were tested: two permanent (Ash Split Cath 14Fr, 28cm; Tesio 10Fr, 30cm (Medcomp, Harleyville, PA, U.S.A.) and two acute (Duo-Flow 11.5Fr, 20cm; Duo-Split 12.5Fr, 20cm (Medcomp)).

These catheters differ not only in number and position of side holes, but also in basic geometry. The Ash Split Cath and Duo-Split are both double-D catheters [17]. The difference between these two catheters lies in the number of larger side holes: 2 in Ash Split Cath and 6 in Duo-Split. They both have a circular tip lumen with smaller diameter, but the Ash Split Cath has 6 small side holes and the Duo-Split has none. Twin Tesio catheters come with identical single-lumen pairs, each with 6 side-holes laid out in a spiral pattern. The Duo-Flow is a coaxial catheter with tapered venous tip and 4 side holes for each lumen.
Different test runs were performed for each catheter: once with the actual catheter and then with some side holes masked with tape, thus effectively preventing any flow through them. For both Ash Split Cath and the Tesio catheters, all side holes were closed; for Duo-Split and Duo-Flow catheters, only two side holes in each lumen were masked because, otherwise, the flow rate would become too restricted in the Duo-Split and impossible for the Duo-Flow.

RESULTS

As an example, in Fig. 2 the fitted parabolic equations for Ash Split Cath measurements are shown, together with averaged data points. The fit lines follow the data points closely, with good correlation indices and small standard errors on the fit line parameters (a,b). Black symbols signify open side holes and white symbols closed holes. All curves lie close together; pressures are somewhat elevated with side holes closed.

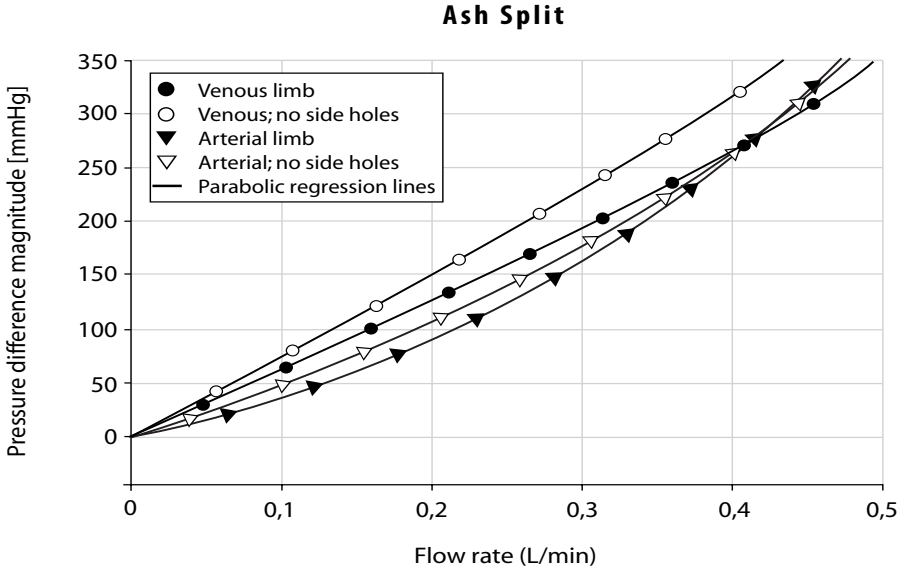

Figure 2. *Measured and fitted quadratic pressure-flow relationships in both limbs (arterial: triangle; venous: circle) of the Ash Split catheter with (filled) and without side-holes (hollow).*

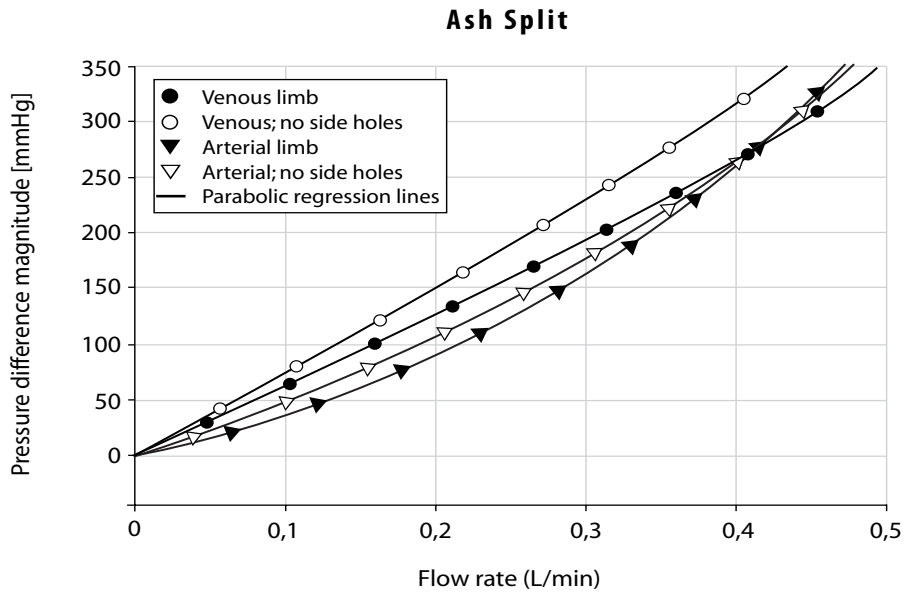

Figure 3. *Hydraulic resistance in Tesio twin catheters (arterial: triangle; venous: circle) is a linear function of the flow rate. At higher flow rates higher resistances are found. Closing of the side holes (hollow) shifts the regression lines obtained with open side holes (filled) upwards, but does not alter the slope.*

The arterial curves (triangles) initially lie below the venous curves, perhaps due to their shorter length; however, due to extra pressure losses, the arterial curves are more quadratic and overtake the venous curves at around 400 ml/min. As an example of hydraulic resistance, the results for the Tesio twin catheters are plotted in Fig. 3.
In this measurement, the hydraulic resistance of arterial limbs is lowest at low flow rates, and highest at moderate to high flow rates. It should be noted that the effect of closing the side holes is expressed in the upward shift of the curves, which the greatest effect in the arterial limb. This signifies that the y-intercept (constant a, Eq. (2)) has been increased by about 15% - 20%. As the quadratic content (influence of parameter b) in this catheter is small for the usual range of flow rates, this limited increase in intercept has only a mild effect on pressure drop (Eq. (1)).
The calculated D_e's are listed in Table1.

Table 1. The equivalent diameters of the catheters for both limbs (in millimetres)

Catheter	Holes	Arterial	Venous
Ash Split	Open	1.79	1.83
14Frx28cm	All Closed	1.77 (-1%)	1.77 (-3%)
Tesio	Open	1.79	1.81
2x10FRx30cm	All Closed	1.70 (-5%)	1.76 (-3%)
Duo Split	Open	1.42	1.47
12.5Frx20cm	Two Closed	1.10 (-23%)	1.47 (0%)
Duo Flow	Open	1.38	1.45
11.5Frx20cm	Two Closed	1.15 (-17%)	1.45 (0%)

A clear distinction can be made between the larger and longer permanent catheters and the shorter and smaller acute catheters. The permanent catheter group has an D_e of about 1.8 mm (internal diameter). A tube with this size and an assumed typical wall thickness of 0.5 mm would correspond to about 8.5 Fr (outer diameter). The acute group has much lower D_e's, about 1.45 mm. (about 7.5 Fr OD). Closing the side holes has nearly no effect in permanent catheters (maximum decrease of 5%) or in the venous limb of acute catheters. However, for the arterial limb of acute catheters, D_e decreases significantly (about 20%) when two holes are closed. Since in all catheters except the Duo-Flow, the tip geometry of both limbs is equal, and since this tip geometry has a major impact on the performance, the same De is expected in each of these catheters. A small difference of 1% - 3% in favor of the venous limb is observed as outflow produces no or smaller special pressure losses compared to inflow. The absolute value of the pressure drop over the length of catheters at a test fluid rate of 300 ml/min is listed in Table II.

Table 2. The pressure drop (mmHg) over the catheter at 300ml/min.

Catheter	Holes	Arterial	Venous
Ash Split	Open	1.79	1.83
14Frx28cm	All Closed	1.77 (-1%)	1.77 (-3%)
Tesio	Open	1.79	1.81
2x10FRx30cm	All Closed	1.70 (-5%)	1.76 (-3%)
Duo Split	Open	1.42	1.47
12.5Frx20cm	Two Closed	1.10 (-23%)	1.47 (0%)
Duo Flow	Open	1.38	1.45
11.5Frx20cm	Two Closed	1.15 (-17%)	1.45 (0%)

Again, a distinction can be made between acute and permanent catheters: in the latter, the pressure difference is usually below 200 mmHg, except when side holes are closed. However, even in this case, the increase in pressure difference is minor.
In acute catheters, pressure differences greater than 300 mmHg are needed to maintain flows. We measured the flow rates that can be obtained with a reasonable pressure drop of 200 mmHg over the catheter length (Table III). In the permanent catheters, a flow rate of over 300 ml/min is easily attained, but becomes slightly lower when the side holes are occluded. Contrary to what Table I may suggest, there is a performance difference between the coaxial catheter (Duo-Flow) and the double-D shaped design (Duo-Split). Without occlusion of the side holes, the former attains a 10% (venous limb) to 25% (arterial limb) lower flow rate than the latter.

Table 3. The flow rate (ml/min) through the cannula at a pressure drop of 200 mmHg.

Catheter	Holes	Arterial	Venous
Ash Split	Open	337	322
14Frx28cm	All Closed	330 (-2%)	286 (-11%)
Tesio	Open	290	303
2x10FRx30cm	All Closed	250 (-14%)	274 (-10%)
Duo Split	Open	209	198
12.5Frx20cm	Two Closed	99 (-53%)	196 (-1%)
Duo Flow	Open	155	178
11.5Frx20cm	Two Closed	92 (-41%)	169 (-5%)

DISCUSSION

Our *in vitro* study comparing the performance of double-lumen HD catheters demonstrates that the De derived from the pressure-flow relationship in permanent catheters is larger than the diameter of acute catheters. Generally, in medical and dialysis-related literature, the pressure-flow relationship is described by Poiseuille's equation [22], which states that the pressure difference varies linearly with the flow rate and is inversely proportional to diameter to the fourth power. While this is true for the ideal case of a Newtonian fluid flowing through a circular tube, and neglecting end effects, this is not the true for catheters. Although double-D shaped lumens also render a linear relationship as described by Poiseuille. The deviation from linearity in catheters is related to the extra pressure losses that occur at the entrance and exit of the catheter. Inflow through, or outflow from, side holes and tapered tips creates local velocity changes both in direction and magnitude. Hence, the pressure-flow relationship is a quadratic, as shown for the Ash Split Cath in Fig. 2. The D_e's (Table I) may seem rather small compared to actual diameters (*e.g.* Tesio 8.5 Fr versus 10 Fr advertised). The reason for this phenomenon relates to the fact that D_e is based on performance characteristics, which include the effect of extra in- and outflow pressure losses.

The total pressure difference is the sum of the Poiseuillian flow resistance, which increases linearly with the flow rate and the effect of the extra resistance at the infow or outflow, which is proportional to the flow rate squared. According to Eq. (3), an increased pressure difference renders a lower D_e.
The concept of De is an interesting one, as it is a single parameter that allows to comparison of pressure-flow data of different catheters independently from the test fluid used (and thus also independently of hematocrit and viscosity) and the length of the catheter. Longer catheters evidently require a higher pressure difference for equal flow rates. Therefore, the D_e is a direct measure of the performance of a catheter's design. This is especially useful for dual-lumen catheters as, for some designs (co-axial, double-D shaped), there exists no clear definition for the diameters of the individual limbs, which makes it harder to compare their geometrical data with two independent single-lumen catheters, such as, for example, the Tesio twin set. Catheters with the same lumen diameter and the same length but with a different D_e differ by the level of their specific pressure losses at in- and outflow. This may also be an indication for elevated shear stresses in these zones, which may affect the survival of blood cells.
For HD, 300 ml/min is recommended as the minimum value for effective treatment [5]. Therefore, we tabulated (Table II) the required pressure differences over the catheter length (some extra pressure drop is generated in the dialysis circuit towards the blood pump). If patients have a lower Hct due to anemia, this pressure difference decreases proportionally with the actual blood viscosity. In the acute catheters, pressure differences greater than 300 mmHg are required. These are not easily attained, even in modern dialysis equipment. It is very difficult, especially in the arterial limb, to attain 300 ml/min, as the very low pre-pump pressures that are needed would severely limit the actual blood flow rate [22]. The pressures required to draw 300 ml/min through acute catheters with a reduced number of side holes are completely out of range. This indicates the weak point of these catheters: development of a fibrin sleeve over catheter's tip or thrombus formation near the side holes would severely limit the flow rate through these holes and consequently through the catheter as a whole.
As already indicated in Fig. 2, the results in Tables I-III clearly show that closing the side holes of permanent catheters, or the venous limbs of the tested acute catheters, has only a very minor effect on the performance of the catheter. Side holes are required, however, at the inflow tip of acute catheters. The decrease in flow rates shown in Table III, especially in the arterial limbs of the tested acute catheters, may be due partly to the difference in actual diameters (11.5 Fr Duo-Flow and 12.5 Fr Duo-Split result in 3% difference in D_e), but the much larger difference in flow rate (-25%) for the arterial lumens between these two catheters is by design. Coaxial catheters generally have poor performance of the arterial (outside) lumens. The effect on the pressure differences, listed in Table II, may seem somewhat higher than the differences showed in the Tables I and III, but this is merely an indication that a small diameter change has a much greater effect on pressure difference due to the fact that pressure difference is inversely proportional to diameter to the fourth power. For example, a 2.5% decrease in diameter will cause a 10% increase in pressure difference.

The findings in this study imply that side holes can be eliminated from permanent catheters, and that the number of side holes may be decreased in the venous limbs of acute catheters. Use of side holes may provoke other problems as well. It has been reported that the vein intima may be sucked into the lumen of the catheter through the side holes, especially when the tip hole is obstructed [19]. Side holes may enhance recirculation between the limbs of dual-lumen catheters, which triggers the manufacturers to separate the lumen tips or to position the side holes on opposite sides [17]. Leaching of locking solutions may enhance the formation of blood cloths as is frequently observed at the tip and side holes of catheters [19]. When vein intima is sucked, the pre-pump pressure and, consequently, blood flow through the dialysis machine decrease significantly.
As recirculation is a dynamic process that depends not only on the geometrical design of the catheter, but also on its position in the vicinity of the right atrium and on cardiac input flow [23], it currently cannot be determined in our model. For similar reasons, it is difficult to use these data to comment on the leaching of anticoagulants between treatments [19], as this process depends on catheter tip movement and position in the right atrium [24] and density differences between blood and locking solution. One last disadvantage of catheter side holes is the formation of blood clots. Clots may be firmly anchored to the walls around side holes [18,19]. As some of these holes have a small diameter and therefore a much greater wall surface-to-flow area ratio, only limited force can be applied to remove the clots in situ. The clinical importance of potential problems caused by side holes is not clear. It should be noted that performance might not be the only reason to use side holes in catheters. No information about their use and performance as a backup for (partial) occluded or malpositioned of catheters is known to us. However in our view, occluded tips should always be opened, for a cloth or fibrin sleeve may be the cause of hemolysis [25]. Tips that are stuck against the wall can be freed by applying positive pressure on the limb. Malpositioned catheters tips will always have less than optimal performance. Preliminary studies comparing permanent catheters, with limited patient-catheter days, did not show an important advantage with different tip designs [26]. For permanent catheters, where the side holes do not increase the performance and therefore have limited blood flows through them, with zones of low shear, clot attachment may possibly be enhanced [15].

CONCLUSION

Our analysis of different catheters for hemodialysis treatment demonstrates that multiple side holes, generally and under the ideal circumstances of the presented *in vitro* setup, do not improve catheter performance, except for inflow in acute catheters.
The equivalent diameter derived from the pressure-flow relationship of permanent catheters is larger than the diameter of acute catheters, and double-D catheters perform better than coaxial designs. These findings should be taken into account when developing new catheters. More clinical studies are needed to confirm the implications of our findings in the practice hemodialysis.

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6a Reduction of hemodialysis catheter related complications by locking solutions

Superior antimicrobial activity of trisodium citrate over heparin for catheter locking.

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ABSTRACT

Background. Haemodialysis catheters used for vascular access are frequently complicated by infection and catheter-related thrombosis. Improvement of interdialytic locking solutions could reduce these problems. Trisodium citrate (TSC) has been advocated in recent years because it might have antimicrobial qualities.

Methods. Antimicrobial efficacy of four concentrations of TSC (2.2, 7.5, 15 and 30%) was compared with three equi-osmolal sodium chloride (NaCl) concentrations, unfractionated heparin 5000 IU/ml and a solution of gentamicin 1 mg/ml in TSC 7.5%. We analysed antimicrobial properties by two classical in vitro susceptibility tests. All tests were performed in triplicate by incubation of test fluids with Staphylococcus aureus, Staphylococcus epidermidis, Escherichia coli, Pseudomonas aeruginosa and Candida albicans.

Results. Increasing TSC concentrations effectively killed the staphylococcal strains in both assays. For E.coli and P.aeruginosa complete killing was achieved only with TSC 30%. TSC 30% was also the only solution that significantly inhibited growth of C.albicans. Heparin manifested no antimicrobial effect of any significance. Adding gentamicin to TSC provided superior bacterial growth inhibition but had no effect on yeast growth. TSC solutions manifested superior antimicrobial activity compared with iso-osmolal NaCl solutions in both assays.

Conclusion. This *in vitro* study demonstrates superior antimicrobial activity of TSC, especially in higher concentrations, in contrast to heparin. The mechanism seems to differ from hyperosmolality. Ca 2^+ and Mg 2^+ chelating effects are probably more important. Adding gentamicin provided the most potent antimicrobial solution. However, for reasons concerning development of bacterial resistance and sensitization of the patient, continuous exposition to aminoglycosides seems not advisable.

INTRODUCTION

Vascular access is a major factor of concern for patients on hemodialysis treatment. Despite the recommendations of the National Kidney Foundation – Dialysis Outcome Quality Initiative Clinical Practice Guidelines for Vascular Access that recommends placement of an arteriovenous access before initiation of chronic hemodialysis treatment, the use of catheters for hemodialysis access is substantial [1]. Stehman-Breen reported from the United States Renal Data System 1996 that 66% of patients with end stage renal disease started hemodialysis treatment with a catheter for access to the blood stream [2]. Twardowski reported that 24.3% of almost 30,000 hemodialysis treatments in his outpatient facility in the period 1995 to 1997 were performed with a tunneled cuffed catheter [3]. The use of hemodialysis catheters, however, is associated with an important risk for catheter-related infection and insufficient dialysis due to flow problems with or without intraluminal thrombosis [4]. Especially vascular access-related infections, mostly associated with hemodialysis catheters, have emerged as an important cause of morbidity and mortality in hemodialysis patients. From a prospective study in 796 hemodialysis patients performed in seven outpatient hemodialysis centers in 1998, Tokar *et al*. calculated that over 92,000 episodes of vascular access infection occur annually among 220,000 prevalent hemodialysis patients in the US. A third of these patients had to be treated by hospitalization because of the infection. In addition, patients with a catheter had a relative risk for infection of 2.07 compared to patients with an arteriovenous fistula of graft [5].

It is recognized that microorganisms can adhere to the surface of a catheter. Contamination of the catheter hub, subsequent colonization of catheters with microbes and formation of a biofilm produced by bacteria are thought to be major riskfactors for both catheter-related infections and intraluminal thrombosis [6]. It is, however, not elucidated whether the most important mechanism of catheter related bacteremia is extraluminal or intraluminal colonization. If catheter-related blood stream infections are mainly secondary to intraluminal colonization, interdialytic locking using a solution with extensive antimicrobial effects can provide an important reduction of these complications. Traditionally heparin 5000-10.000 IU/ml is used for interdialytic locking of hemodialysis catheters. Recently, however, trisodium citrate (TSC) has been proposed for catheter locking [7] and TSC 30% is already used in clinical practice [8]. TSC provides local anticoagulation by binding $Ca^{2}+$. It can have important advantages over heparin, such as prevention of heparin-induced side-effects and unintentional systemic heparinisation that can lead to bleeding complications, as was recently shown by Kaaraslan *et al*. [9]. An additional factor in favor of TSC is its potential antimicrobial property. For these reasons TSC has been advocated for hemodialysis catheter locking and distributed temporarily by a hemodialysis catheter manufacturer (Medcomp, Medical Components Inc., Harleysville, PA, USA). The level of hyperosmolality of the solution was considered the main explanation responsible for antimicrobial activity although binding of divalent cations was also mentioned [7].

However, very limited *in vitro* data on the antimicrobial properties of TSC as hemodialysis catheter locking solution are presently available. It is also not clear whether antimicrobial potency of a solution depends on the level of hyperosmolality or not.

The purpose of this study is to evaluate the *in vitro* antimicrobial activity of different concentrations TSC and to compare them with heparin and isoosmolal sodium chloride (NaCl) solutions. We employed two classical *in vitro* antimicrobial susceptibility tests and used four bacterial strains and one yeast strain commonly found in catheter-related bacteremia.

METHODS

Antimicrobial efficacy of four concentrations of trisodium citrate (TSC), 2.2% (300 mosmol/kg H^2O), 7.5% (1020 mosmol/kg H^2O), 15% (2040 mosmol/kg H^2O) and 30% (4080 mosmol/kg H^2O) was compared with sodium heparin 5000 IU/ml (300 mosmol/kg H^2O). TSC 7.5% with gentamicin 1 mg/ml (1030 mosmol/kg H^2O) was used to analyze the influence of adding an antibiotic to the solution. As control we used NaCl 0.9%. In Addition we also compared the TSC solutions with isoosmolal solutions of NaCl 0.9% (300 mosmol/kg H^2O), NaCl 6.1% (2040 mosmol/kg H^2O) and NaCl 12.2% (4080 mosmol/kg H^2O). All solutions were manufactured from raw base by the department of Pharmacy of the Vrije Universiteit Medical Center, Amsterdam, the Netherlands. The solutions were heat sterilized for 16 min at 121ºC and the pH was controlled between 6.4 and 7.5. Gentamicin sulphate was obtained from commercially available vials (Gentamicin CF, Centrafarm Services, Etten-Leur, the Netherlands).
All tests were performed with five standardized reference strains from the American Type Culture Collection (ATCC, Manassas, VA, USA); *Staphylococcus aureus* (ATCC 25923) *Staphylococcus epidermidis* (ATCC 12228), *Pseudomonas aeruginosa* (ATCC 25922), Escherichia coli (ATCC 27853) and *Candida albicans* (ATCC 90028).
The antimicrobial activity of the solutions was investigated by time-kill and agar diffusion methods, essentially performed according to National Committee for Clinical Laboratory Standards guidelines [10]. Briefly, logarithmic-phase bacterial and yeast cultures were used for the final inoculum of 10^5 colony-forming units per ml (cfu/ml). Twenty µl of the microbial suspension was added to 2000 µl of a suspension containing a 10:1 dilution of the test solution in trypticase soy base (TSB) broth (Difco Laboratories, Sparks, MD, USA) to achieve a final bacterial concentration of 10^3 cfu/ml. At this initial concentration, the comparison with time-kill curves of control solution was best feasible. Tubes were incubated at 37º Celsius (C). At the start of the experiment (t=0) and at 1, 2, 4 and 24 hours 50µl of this suspension was plated on blood agar plates (BA) (Oxoid, Basingstoke, Hampshire, UK) supplemented with 7% sheep blood (Bio Trading, Mijdrecht, the Netherlands). Subsequently, plates were incubated for 24 hours at 37º C. Afterwards colonies were counted and time-kill curves constructed from calculated cfu/ml. All tests and cultures were done in triplicate.
The agar diffusion susceptibility test was done analogous to the disk diffusion test (Kirby-Bauer) [10]. BA and TSB plates were seeded with a bacterial solution with a final inoculum of 10^5 cfu/ml. Separate plates were used for each of the five microbial strains. Instead of using disks impregnated with test solution, one well with a diameter of 8 mm was punched out of the agar at the center of the plate. The well was filled with test solution and this was repeated every two hours for the first 6 hours of incubation. A total of 0.45 ml of test solution had to be added to the well to keep it filled.

Plates were incubated at 37º C for 24 hours. Afterwards zones of inhibition around the well were measured. All tests were done in triplicate with BA and TSB plates. Statistical analysis was performed with SPSS software package 9.0 (SPSS Inc., Chicago, Ill, USA) with repeated-measurements analysis of variance for time-kill curves. Chi-square analysis was performed for means of bacterial colony forming units at t=24 hours and for zones of inhibition achieved from the agar diffusion test. Significance of test results was based on $p<0.05$ on a two-tailed test.

RESULTS

Antimicrobial properties of different locking solutions

Time-kill studies

The time-kill curves for heparin, all concentrations of TSC and the combination of TSC with gentamicin are presented in figure 1. Heparin showed some growth inhibition of *S. aureus* and *S. epidermidis* compared to control (NaCl 0.9%). However, after 24 hours all strains showed increasing growth (upward directed slope) when incubated with heparin. Heparin had no significant effect on growth of gram-negative bacteria and *C. albicans* compared to control.
TSC 15% and TSC 30% reduced the number of cfu/ml of all strains over 24 hours compared to the concentration at start of the experiment except for the yeast *C. albicans* and except for *P. aeruginosa* with TSC 15%. The citrate solutions inhibited growth of all strains compared to control (NaCl 0.9%), including Candida. The gram-negative strains *E. coli* and *P. aeruginosa* were only adequately affected by the highest concentrations of TSC (15% and 30%)($p<0.05$ for T=24 hours). There were no statistically significant differences between TSC 30% and TSC 15%. TSC 30% was more effective in growth reduction of E. coli, P. aeruginosa and C. albicans than heparin. ($p<0.05$ for T=24 hours)

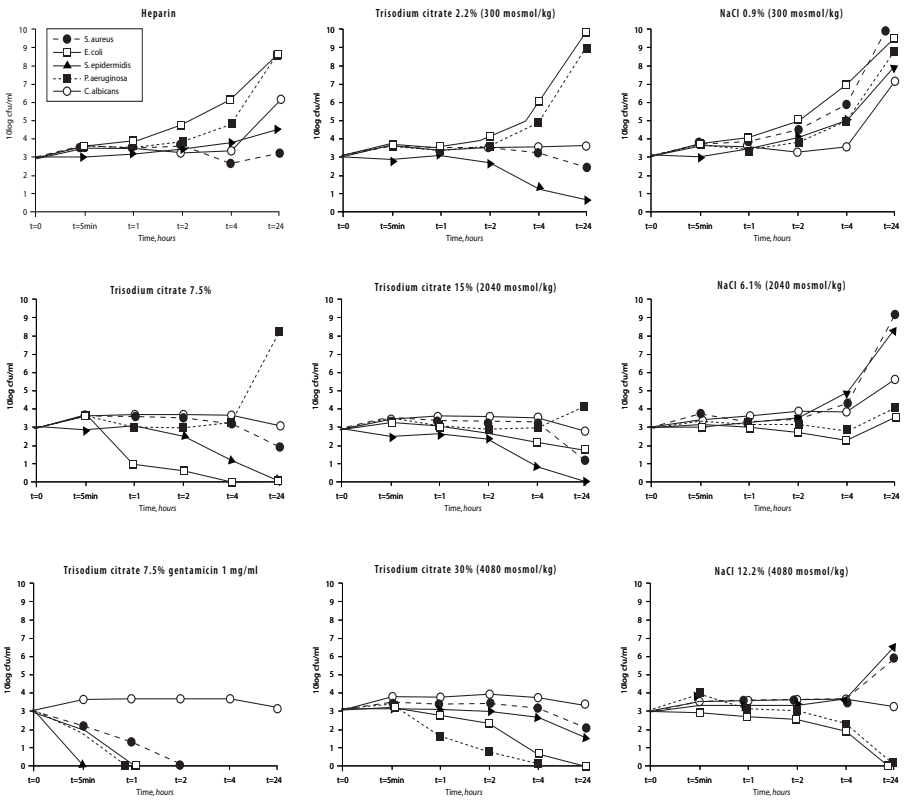

Figure 1. *Time-kill curves for heparin, trisodium citrate and isoosmolal NaCl solutions and the combination of trisodium citrate 7.5% with gentamicin. Tested microbial strains are Staphylococcus aureus (ATCC 25923), Staphylococcus epidermidis (ATCC 12228), Pseudomonas aeruginosa (ATCC 25922), Escherichia coli (ATCC 27853) and Candida albicans (ATCC 90028).*

Agar diffusion susceptibility test (figure 2)

Studies using TSB plates and BA plates revealed similar results. The results for the zones of inhibition were therefore pooled for further analysis. Zones of inhibition are given in figure 3. For all microbial strains no growth inhibition by the control solution (NaCl 0.9%) was found. Heparin also showed no effect at all.

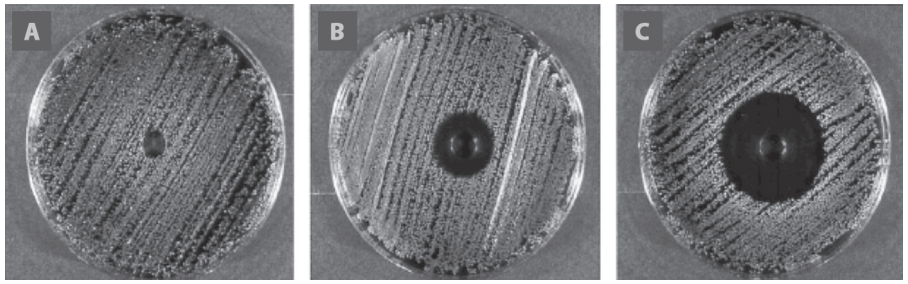

Figure 2. *Agar diffusion susceptibility test. Bloodagar plates seeded with Staphylococcus aureus and wells filled with heparin (A), trisodium citrate (TSC) 7.5% (B) and trisodium citrate 30% (C) after 24 hours at 37°C showing larger zones of bacterial killing for TSC solutions.*

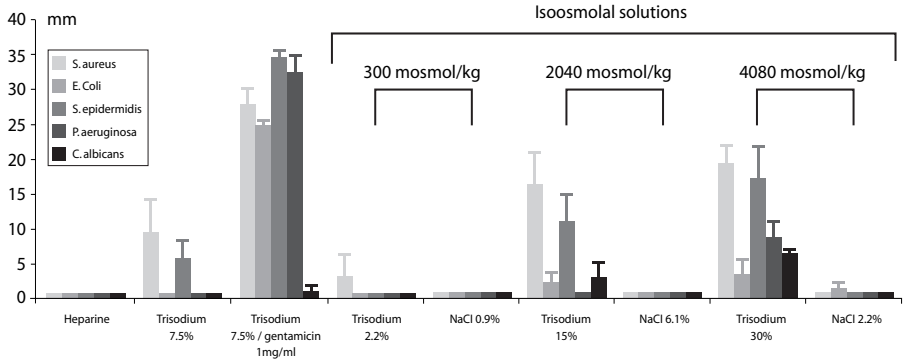

Figure 3. *Zones of inhibition for the agar diffusion susceptibility test for heparin, trisodium citrate and isoosmolal NaCl solutions and the combination of trisodium citrate 7.5% with gentamicin. Values are means + SD. Tested microbial strains are Staphylococcus aureus (ATCC 25923), Staphylococcus epidermidis (ATCC 12228), Pseudomonas aeruginosa (ATCC 25922), Escherichia coli (ATCC 27853) and Candida albicans (ATCC 90028).*

In general, higher concentrations of TSC demonstrated increasing inhibitory effect on all strains (figure 3). TSC 30% was the only solution to inhibit growth of all tested microbes including *C. albicans*. The inhibition zone was significantly larger for all strains compared to control (NaCl 0.9%) and heparin ($p<0.01$ for all comparisons).
Addition of gentamicin to TSC potentiated the effect of TSC on all bacterial strains in both the dilution and the diffusion test. Growth of *C. albicans*, however, was not influenced.

ANTIMICROBIAL PROPERTIES OF ISOOSMOLAL SOLUTIONS

Time-kill studies

Comparing the results of the time-kill curves of isoosmolal solutions, it is clear that there are major differences (figure 1). For the isoosmolal solutions NaCl 0.9% and TSC 2.2%, TSC 2.2% provided stronger growth inhibition in *S. epidermidis*, *S. aureus* and *C. albicans* ($p<0.05$). The growth at 24 hours was inhibited significantly better for *S. epidermidis* and *S. aureus* by TSC 15% compared to NaCl 6.1% and for *S. epidermidis* and *S. aureus* by TSC 30% compared to NaCl 12.2%. For the other strains the time-kill curves were not significantly different.

Agar diffusion susceptibility test

The agar diffusion test also showed larger zones of inhibition for TSC compared to isoosmolal NaCl solutions, especially when osmolality increased (figure 3). NaCl 6.1% and NaCl 12.2% exhibited no significant effect on microbial growth over NaCl 0.9%. NaCl 0.9% did not inhibit growth of any microbial strain. In contrast, isoosmolal TSC 2.2% inhibited growth of *S. aureus* significantly. TSC 15% showed more antimicrobial effect compared to isoosmolal NaCl 6.1% in all strains except for *P. aeruginosa* ($p<0.05$). For the isoosmolal solutions with the highest osmolality, NaCl 12.2% and TSC 30%, superior growth inhibition of TSC 30% was found in all strains ($p<0.01$).

DISCUSSION

In the present study we investigated the antimicrobial activity of TSC against five different microorganisms frequently encountered in catheter-related infections in hemodialysis patients using two standardized antimicrobial susceptibility tests. The antimicrobial activity was dose dependent with the highest efficacy for TSC 30%. In both tests the antimicrobial activity of TSC exceeded that of isoosmolal NaCl concentrations, whereas heparin manifested only minimal antimicrobial activity. Thus it can be concluded that the use of high concentrations of TSC for catheter locking could have an advantage over heparin. Adding gentamicin to TSC provided the most potent antibacterial solution. Lynn (*Lynn, J Am Soc Nephrol* 2000; 10:1006A), however, showed that locking with a mixture containing an antibiotic results in low systemic concentrations of the antibiotic resulting from diffusion from the tip of the catheter. The development of bacterial resistance and sensitization of the patient can be the consequence. Addition of aminoglycosides or other antibiotics to locking solutions for long-term use is therefore not advisable. Heparin revealed no relevant anti-microbial activity. This was recently also reported by Capdevila *et al*. *in vitro* by means of the time-kill curves method and *in vivo* by implanting catheters in rabbits and inducing secondary infection but they only used one strain of *S. aureus* [11].

To investigate whether a locking solution can reduce complications, only a clinical study with large numbers of patients can provide definitive answers. The present study only provides *in vitro* data, but these studies have to be performed to give direction to which locking solution is most likely to reduce complications before conducting a clinical trial. No standardized methods are available for testing antimicrobial activity of catheter locking solutions. Although other in vitro methods have been advocated in the past, seldom tests were performed using validated techniques with more then one microorganism and mainly established antibiotics were added to solutions for locking [11;12]. The methods we applied for this study consisted of two widely validated and recommended antimicrobial susceptibility tests . The tests were performed as recommended by the National Committee for Clinical Laboratory Standards [10;13]. Dilution tests are employed to provide more exact information on the concentrations of the antimicrobial solution that cause growth reduction and killing. However, the standardized disk diffusion test is the initial susceptibility test used in most laboratories because of its ease of performance, reproducibility, and proven value as a guide to antimicrobial therapy [14]. This test demonstrated the pronounced antimicrobial properties of TSC 30% most distinctly.

For the present study we selected both gram-positive and gram-negative bacteria frequently involved in catheter-related bacteremia. *S. aureus* and *S. epidermidis* are the most common bacteria found in catheter-related bacteremia. However, gram-negative bacteria can be isolated in up to 45% of cultures and up to 21% of cultures reveal a polymicrobial infection [15]. We used reference microbial strains from the ATCC to minimize the variable microbial properties that may affect the results. Microorganisms were seeded on bloodagar and trypticase soy based plates to investigate the influence of the growth medium. The results were very similar for both plates. Yeasts are not commonly involved in catheter related infections. Nevertheless we included a *Candida albicans* strain in our study because of the high mortality of systemic yeast infection. Inhibition of growth of *Candida spp*. by a locking solution could therefore be of importance.

Both susceptibility tests showed clear differences in antimicrobial properties for isoosmolal solutions. In 18 of 30 comparisons that could be made between isoosmolal TSC and NaCl solutions, TSC exhibited significant greater inhibitory effects on microbial growth. Therefore, the anti-microbial properties of higher concentrations of TSC can not be attributed to hyperosmolality. It is likely that other effects of TSC like chelation of the divalent cations Ca^{2+} and Mg^{2+} are more important. From dentistry research it is known that Ca^{2+} and Mg^{2+} chelating agents like disodium-ethylenediaminetetraacetate (EDTA) and sodium citrate exhibit similar inhibition of growth and coaggregation of microorganisms. Root *et al*. showed in an *in vitro* model with catheter segments incubated with 10^3 *S. epidermidis* that EDTA provided total killing of bacteria [16]. They suggested that especially chelation of Mg^{2+} can interfere with cellular integrity by degradation of the bacterial cell wall membrane. Lipopolysaccharides in the bacterial cell wall are crossed-linked with divalent cations, providing stability. Lowering the concentration of these cations can lead to disruption of the cell wall and increase permeability [14;17]. Consistent with these findings is the observation that sodium citrate proved to be a potent permeabilizer of the cell wall at millimolar concentrations in a model used for permeability changes in gram-negative bacteria. The effect was partly (*P. aeruginosa, S. typhimurium*) or almost totally (*E. coli O157*) abolished by $MgCl_2$, suggesting that part of the action occurs by chelation [17].

Apart from Mg^{2+} -binding, removal of Ca^{2+} from the surrounding milieu can be an explanation for the antimicrobial properties of TSC. Ca^{2+} may regulate several genes

responsible for growth and survival of microbes. Holland *et al*. demonstrated that cell division in *E. coli* in particular appears to be very sensitive to the level of cellular Ca^{2+}, with the frequency of division clearly reduced by incubation with EDTA and by verapamil, a Ca^{2+}-channel inhibitor. The effect of EDTA was clearly correlated with depletion of cellular Ca^{2+} [18]. Biofilm formation, thought to be a key factor in catheter colonization and ultimately bacteremia, is probably dependent on Ca^{2+}. A biofilm consists of bacteria that attach to surfaces and aggregate in a hydrated polymeric glycocalyx matrix of their own synthesis. Formation of these sessile communities and their inherent resistance to antimicrobial agents allows microbes to survive in a hostile environment.
Even in individuals with excellent cellular and humoral immune reactions, biofilm infections are rarely resolved by the host defense mechanisms. In addition antibiotics are not very useful because they have been shown to penetrate poorly into a biofilm [19]. Furthermore at least some of the microbial cells in a biofilm experience nutrient limitation and therefore exist in a slow-growing state. Slow-growing or non-growing microbial cells are not very susceptible to antimicrobial agents. Until recently, the bacterial glycocalyx was regarded as being homogeneous in construction and static in its structure. It is now recognized that glycocalyces are not structurally static, but rather responsive to the chemical composition of the surrounding milieu. An increasing environmental Ca^{2+}-concentration dramatically enhanced the survival of *P. aeruginosa* in biofilms upon a 12-hour exposure to tobramycine in an in vitro experiment [20]. It was suggested that Ca^{2+}-induced crystallization of the glycocalyx resulted in decreased permeability of the biofilm for small molecules like aminoglycosides. In summary, chelation of Ca^{2+} and Mg^{2+} by TSC may prevent the formation of a biofilm that consists of microbes in a firm glycocalyx. Reduction of the incidence of catheter-related bacteremia by the intraluminal route could be the result. This hypothesis was tested in some *in vitro* models with catheter segments but the constructions with catheters or fragments trying to imitate the clinical situation are artificial [21;22].
As stated before, this study only provides data from *in vitro* antimicrobial susceptibility tests. It is not clear if the results can be translated to general practice as numerous factors have been implicated in the pathogenesis of catheter-related bacteremia. For that reason, locking solutions must be compared in a clinical study to confirm their benefit. So far, only few comparative studies have been published showing no clear differences between TSC and heparin [8;23]. These studies, though, only accounted about 5000 catheter-days pooled data and mostly used lower concentrations TSC. With a rate of 3-5 infections per 1000 catheter-days it is obvious that larger studies are needed to find a significant difference.
Ash *et al*. reported their experience in a hemodialysis patient cohort of 70 patients with 60% tunneled cuffed catheters [7]. After introduction of TSC 23-47% for catheter locking they observed an average decline of 4.5% of all patients per month having a bacteremia to zero percent. Recently, Stas *et al*. reported a study comparing heparin 5000 IU/ml and TSC 30%. Thrombus formation in the catheter was evaluated after 201 interdialytic locking periods; no significant differences could be demonstrated [8]. In both studies no clinically relevant side effects occurred during instillation of hemodialysis catheters with TSC.
This is important, as concern has risen of using TSC for locking catheters after a fatal

accident [24]. In this particular case, however, a large amount of TSC was injected in a previously unstable patient with severe electrolyte disturbances. It is clear that the use of these solutions should be restricted to authorized and skilled health care professionals.
We conclude that in our *in vitro* study using standardized antimicrobial susceptibility tests we demonstrated that trisodium citrate 30% was the most potent antimicrobial locking solution and that its hyperosmolality was of minor importance to explain the inhibitory effects of TSC on microbial growth. However before introduction in practice, randomized clinical trials should confirm the benefit.

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6b Reduction of hemodialysis catheter related complications by locking solutions

Randomized clinical trial comparison of trisodium citrate 30% and heparin as catheter-locking solution in hemodialysis patients.

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ABSTRACT

Background. Interdialytic hemodialysis catheter-locking solutions could contribute to a reduction of catheter-related complications, especially infections. However, they can cause side effects because of leakage from the tip of the catheter. Recently, trisodiumcitrate (TSC) has been advocated because of its antimicrobial properties and local anticoagulation.

Methods. In a multicenter, doubleblind, randomized, controlled trial, TSC 30% was compared with unfractionated heparin 5000 U/ml for prevention of catheter-related infections, thrombosis, and bleeding complications.

Results. The study was stopped prematurely because of a difference in catheter-related bacteremia (CRB; $P < 0.01$). Of 363 eligible patients, 291 could be randomized. The study included 98 tunneled cuffed catheters and 193 untunneled. There were no significant differences in patient and catheter characteristics on inclusion. In the heparin group, 46% of catheters had to be removed because of any complication compared with 28% in the TSC group ($P = 0.005$). CRB rates were 1.1 per 1000 catheter-days for TSC versus 4.1 in the heparin group ($P < 0.001$). For tunneled cuffed catheters, the risk reduction for CRB was 87% ($P < 0.001$) and for untunneled catheters was 64% ($P = 0.05$). Fewer patients died from CRB in the TSC group (0 versus 5; $P = 0.028$). There were no differences in catheter flow problems and thrombosis ($P = 0.75$). No serious adverse events were encountered. Major bleeding episodes were significantly lower in the TSC group ($P = 0.010$).

Conclusion. TSC 30% improves overall patency rates and reduces catheter-related infections and major bleeding episodes for both tunneled and untunneled hemodialysis catheters. Flow problems are not reduced.

INTRODUCTION

In 2001, approximately 900 per 1 million population in the United States were treated with hemodialysis for ESRD, and an annual increase of 7.1% is expected until 2010 (1,2). For chronic hemodialysis treatment, an arteriovenous fistula or graft is preferred for vascular access. However, in current practice, the use of hemodialysis catheters is substantial. From recent data of the Dialysis Outcomes and Practice Patterns Study, it is recognized that 60% of incident and 17% of prevalent patients in the United States depend on a catheter for vascular access (3). Such widespread application of catheters exposes patients to an enhanced risk for catheter-related complications such as infection and insufficient dialysis as a result of flow problems (4). Because of these complications, approximately 50% of all catheters have to be removed and/or replaced, resulting in substantial patient morbidity as well as consumption of resources (5). Hemodialysis catheter-related bacteremia (CRB) is the most serious complication, with an average incidence of 3.4 to 6.5 periods per 1,000 catheter-days (5–9). Recently, it was estimated from the United States Renal Data System and the Medicare reimbursement data that in the United States, there are 22,000 to 100,000 cases of CRB annually in the hemodialysis population and that the costs probably exceed $500 million (2,10,11). Catheter-related infections are thought to arise by several different mechanisms. Contamination of the catheter hub and subsequent colonization of catheters by microbes as well as formation of a bacterial biofilm on the external and internal surface are thought to be the major routes for both catheter-related infections and intraluminal thrombosis (12–14). Usually, concentrated heparin is used for catheter locking. However, its efficacy is uncertain, and its use is seldom discussed in guidelines. The recently updated and widely accepted Dialysis Outcome Quality Initiative guidelines of the National Kidney Foundation, for example, do not mention heparin for catheter locking (15). Also, the safety of heparin locking has never been disputed, although it has been demonstrated that heparin causes unintentional systemic anticoagulation and bleeding episodes (16 –18). Antimicrobial locking solutions could be an attractive alternative. It is known from *in vitro* studies that solutions that contain antibiotics can prevent biofilm formation on foreign surfaces (13). However, solutions that contain high concentrations of antibiotics cannot be used in clinical practice for prevention because of side effects (19,20). High-concentration trisodium citrate (TSC) has been advocated for hemodialysis catheter locking because it provides local anticoagulation. In contrast to heparin, it exposes a broad antimicrobial and anti-yeast effect (21). TSC chelates of Ca^{2+} and Mg^{2+} by which it may prevent biofilm formation and colonization (22,23). Currently, there is limited experience with high concentrations of TSC in clinical practice, and the efficacy and the safety of these solutions for improving catheter outcome have yet to be established (24,25). We conducted a multicenter, double-blind, randomized, controlled trial comparing unfractionated heparin 5,000 U/ml with TSC 30% for interdialytic catheter locking.The aim was to determine whether locking with TSC 30% could increase overall catheter patency and reduce catheter-related infections. The secondary aim was to establish the safety and whether a difference in major bleeding episodes could be demonstrated.

MATERIALS AND METHODS

Selection of Patients

The study was conducted from April 2001 until September 2002 in nine dialysis units from the Netherlands and one from Belgium. Two units were situated in an academic center, seven were in a teaching hospital, and one was a private clinic. In the units, the overall average percentage of patients who relied on a catheter for vascular access was 14%. Patients were eligible for enrollment in the study when they were older than 18 yr, were not admitted to the intensive care ward, and experienced chronic or acute renal failure that required hemodialysis treatment by means of a hemodialysis catheter. Only patients with a newly inserted, well-positioned hemodialysis catheter that was expected to be needed for > 1 wk could be included. Catheters were used for hemodialysis treatment only. The specific type and the diameter used were left to the discretion of the interventional physician. The application of national guidelines for dialysis treatment, which state that a femoral catheter should not be used for > 1 wk, that subclavian catheters should be avoided, and that a tunneled cuffed catheter should be used whenever it is foreseen that a catheter would be needed for > 4 to 6 wk, were recommended. Exclusion criteria were suspected heparin-induced thrombocytopenia or heparin-induced thrombosis, systemic bacterial infection, localized infection requiring systemic antibiotics, proven or suspected allergy to heparin or TSC, and pregnancy. Hospitalization was defined as admission for non–catheter-related reasons at any time a catheter was in place.

The study protocol was approved by the institutional review board of each of the 10 participating institutions, with adherence to the Declaration of Helsinki. Written informed consent was obtained from all patients before enrollment.

Study Design

Patients were randomly assigned to have both lumens of their catheter locked with either unfractionated sodium heparin 5000 U/ml or TSC 30%. Inclusion and randomization was performed immediately after insertion by means of a computer-generated list of random numbers in blocks of six and stratified according to the dialysis center and to the type of catheter inserted (tunneled cuffed or untunneled). Patients and investigators were unaware of the treatment assignments. The locking solutions were manufactured from raw base according to standardized pharmaceutical protocols in conjunction with European Pharmacopoeia Guidelines and delivered as 5-ml vials (A.J. Wilhelm, Pharmacist, Department of Pharmacy, VU University Medical Center, Amsterdam, The Netherlands). The solutions were heat-sterilized for 16 min at 121°C, and the pH was controlled between 6.4 and 7.5. There were no external recognizable differences in the solutions except for randomization codes. The randomization codes were kept by the central department of pharmacy; all others involved in the study were blinded.

After the hemodialysis treatment had been completed, each lumen of the catheter was flushed with 10 ml of 0.9% sodium chloride and locked with the locking solution using a volume exactly equivalent to the internal volume of the lumen noted on the catheter. For preventing accidental infusion of the locking solution, the maximum size of the syringes used was 2.5 ml. The syringe had to be filled with the amount of locking solution necessary to lock one lumen of the catheter. Catheter care protocols were according to national guidelines for hemodialysis treatment and included insertion of catheters under strict asepsis by an experienced operator. In addition, these guidelines included catheter exit-site dressing changes after each treatment and catheter manipulations only to be performed by trained dialysis staff wearing masks and sterile gloves. Use of dry gauze dressings and povidone-iodine ointment at the catheter exit site was recommended.

Patients were examined for nasal carriage of *Staphylococcus aureus* on inclusion, and carriers were treated with intranasal 2% mupirocin ointment for 5 d every month. Hemodialysis treatment was performed according to national guidelines with any form of regional anticoagulation being permitted.

Assessment of Outcome

Overall premature catheter removal was defined as any removal needed for a complication such as infection, thrombosis, and catheter breakdown or leakage and unintentional and accidental removals.

Infection

CRB was defined as fever (temperature > 38°C) or cold chills not during a dialysis treatment and at least one positive blood culture and no other obvious cause of infection. In patients who developed signs of bacteremia without symptoms of an alternative source other than the catheter after careful clinical examination by a physician, at least two blood cultures either from the catheter or from a peripheral vein were taken. Subsequently, antibiotics for suspected CRB were given. When a CRB was established, the catheter could be left in place in case of disappearance of fever and clinical recovery on initiation of antibiotic treatment. In patients who did not improve within 48 h or with recurrent bacteremia within 3 wk after stopping antibiotic treatment and without an alternative source, the catheter had to be removed. In case of recurrent bacteremia, only the first period was counted for the analysis.

Exit-site infection was defined as the development of a purulent exudate or redness around the site not resulting from residual stitches. After culturing, antibiotic treatment was recommended for at least 2 wk. In case of no improvement, the catheter had to be removed. CRB-related admissions, defined as admissions solely caused by a CRB, were counted.

Thrombosis

Thrombosis was defined as a persistent inability to run a blood flow of > 200 ml/min despite positional changes of the patient and/or additional flushing. Thrombosis was treated with instillation of urokinase (5000 to 10,000 IU/ml) in both pools with a volume equivalent to the internal volume of the lumen noted on the catheter. After 15 min, the urokinase was withdrawn and the dialysis was continued. When a blood flow of >200 ml/min was not achieved after this procedure, 100,000 to 250,000 IU of urokinase could be infused in 3 h during dialysis according to the protocol of Twardowski (26). In case of total occlusion of the lumen (i.e., no flow when connected to the dialysis

machine), 40,000 IU/h urokinase during 3 h could be infused in the lumen of the catheter. When this was not successful, the catheter was removed or exchanged. Patients could be re-randomized. In accordance with national guidelines, the minimal acceptable blood flow was 200 ml/min; the target was 250 ml/min. The target for dialysis efficacy was a single-pool Kt/V of at least 1.2 per treatment and a urea reduction rate of 65%.

Safety, Tolerability, and Bleeding Episodes

All noxious and unintended reactions to the locking solution were recorded. Patients were asked to report symptoms after each catheter lock procedure. Persistent bleeding from the place of insertion after catheter placement was considered to be apparent when the patient had to stay on the dialysis unit longer than 3 h or when an intervention with intravenous coagulation promoters was needed. Major bleeding episodes were defined as a clinical evident bleeding episode that included a decrease of the hemoglobin level of 3.6 g/dl (2.0 mmol/L) or more or when a blood transfusion was needed. In case of mortality, the cause was recorded and analyzed. All infectious and thrombotic complications and all catheter removals and adverse events reported by the local investigators were re-evaluated by the study coordinators.

Statistical Analyses

Primary analysis was a Cox regression analysis of catheter survival and CRB from the time of randomization (27). Calculation of the required sample size was based on the assumption that TSC would reduce the premature catheter removal rate from 40 to 30%. With a two-sided test, an < level of 0.05, and a power of 80%, the analysis required 200 catheters per group. With this number of catheters, the power to find a 25% decrease in premature catheter removals is 90%, assuming a rate of 20 per 1000 catheter-days and a mean catheter survival of 40 d (28). The analysis of outcomes was performed on an intention-to-treat basis. A three-member data-monitoring committee judged an interim analysis after inclusion of 200 catheters. The study was stopped because a greater than predefined ($P < 0.01$) significant reduction of the bacteremia rate was found by Cox regression analysis with a statistical difference of $P < 0.009$.
The effect of the treatment assignment on catheter survival and bacteremia was determined with stratification according to clinical center and type of catheter and was adjusted for the following prespecified baseline factors: Age, gender, race, years of dialysis, presence or absence of diabetes, malignancy, cardiovascular disease, acute renal failure, hospitalization, use of coumarin, nasal carriage of *S. aureus*. Kaplan-Meier survival curves were constructed (29). Well-functioning catheters at the end of the study observation time as well as catheters that were removed because they were not needed anymore because patients had a functional arteriovenous access, renal recovery, transfer to peritoneal dialysis, or transplantation were analyzed as censored values.
Secondary outcomes, adverse and bleeding events were analyzed by Cox regressions similar to that used in the primary analysis. In case of concurrent CRB and exit-site infection, they were counted as both. We did not add these infections at any time point. All reported *P* values are two-sided.

RESULTS

Baseline Characteristics of Patients

Of 363 eligible patients during the study period, 291 could be randomized: 143 to heparin and 148 to TSC. Thirty-nine patients were unable or unwilling to give informed consent, in 19 patients the catheter had already been flushed or locked with heparin before consent could be obtained, four patients were admitted at the intensive care unit at the time of catheter insertion, three patients were excluded because of age,

Table 1. Base line characteristics of the patients and catheters

Characteristic	TSC Group (n = 148)	Heparin Group (n = 143)
Age (yr; mean ± SD)	61.6 ± 14.8	61.3 ± 16.0
Race		
white (%)	73	71
black (%)	8	11
other (%)	19	18
Male gender (%)	61	56
Years on dialysis (mean ± SD)	1.1 ± 1.2	1.4 ± 1.3
Weekly dialysis frequency		
two (%)	30	30
three (%)	69	70
four (%)	1	0
Cause of ESRD	19	21
diabetes (%)	19	21
glomerulonephritis (%)	24	18
polycystic kidney disease (%)	7	9
other / unknown (%)	50	54
Acute renal failure (%)	26	25
Diabetes (%)	28	31
Cardiovascular disease (%)	53	55
Coumarin use (%)	31	28
Hospitalization (%)	63	64
Immune suppression (%)	16	14
Malignancy (%)	9	6
Staphylococcus aureus carrier (%)	23	23
Catheter days (n)	8431	8116
Tunneled cuffed catheters (n)	50	48
catheter-days (n)	4857	4522
jugular (n)	49	48
right-sided (%)	92	90
femoral (n)	0	0
subclavian (n)	1	0
Untunneled catheters (n)	98	95
catheter-days (n)	3574	3594
jugular (n)	77	69
right-sided (%)	95	91
femoral (n)	20	24
subclavian (n)	1	2

There were no significant differences (at P <0.05) between the two groups in any of the summarized characteristics.

three patients were expected to leave to a nonparticipating hospital within 1 wk, one patient had a contraindication to heparin, in one patient the randomization code was lost, one patient had a catheter inserted with another one left in place, and one patient was considered to need a catheter for < 1 wk after inclusion and was withdrawn before the first locking procedure by the caring physician.
The baseline characteristics of the patients were similar in the two treatment groups (Table 1). A total of 16,547 catheter-days could be analyzed, 9,379 catheter-days in 98 tunneled catheters and 7,168 catheter-days in 193 untunneled catheters. Because of the stratification method, the groups did not differ significantly with respect to the number of tunneled and untunneled catheters. Both tunneled (97 of 98; 99%) and untunneled catheters (146 of 193; 76%) were situated mainly in the jugular position. Subclavian catheters were almost completely absent, and only a limited number of femoral catheters (44 of 291; 15%) were used in this study. A variety of double-lumen silicone and polyurethane tunneled and untunneled catheters were used. Tunneled cuffed catheter types included Ash-split (*n* = 44), Hemo-Cath (*n* = 24), Tesio (*n* = 5; all Medcomp, Medical Components, Inc., Harleysville, PA), and Neostar Circle-C (*n* = 19; Horizon Medical Products, Manchester, GA). Of all untunneled jugular catheters, 140 consisted of a precurved Duoflow (Medcomp) inserted in the low jugular site. This type is known to have relatively low infection rates compared with other types of jugular catheters (8).

Catheter Patency Rates

The percentage of catheters that had to be removed prematurely was 61% lower in the TSC-locked catheters compared with the heparin-locked catheters (28 *versus* 46%; relative risk [RR] 0.57; 95% confidence interval [CI] 0.38 to 0.85; *P* = 0.005; Table 2, Figure 1). The total number of catheters removed prematurely was reduced from 8.1 to 5.0 per 1000 catheter-days in the TSC group. Patency rates for tunneled catheters were much better with TSC versus heparin (RR 0.38, *P* = 0.015). However, in the TSC-treated group, the survival rates of untunneled catheters did not significantly differ from heparin group (RR 0.69, *P* = 0.11). Predictors of premature removal were hospitalization (RR 1.78; 95% CI 1.21 to 2.62; *P* = 0.006) and having an untunneled uncuffed catheter (RR 3.18; 95% CI 2.04 to 4.94; *P* < 0.0001; Table 2).

Infectious Complications

A total of 33 episodes of CRB occurred in the patients who were randomized to heparin locking compared with nine patients who were assigned to TSC (P < 0.001). CRB rates per 1000 catheter-days were reduced from 4.1 in the heparin group to 1.1 for TSC. The RR for CRB was 75% lower in patients with a TSC-locked catheter (95% CI 49 to 88%; P = 0.0002). The only other independent predictors of CRB were age > 65 yr (RR 2.99; 95% CI 1.48 to 6.03; P = 0.002) and male gender (RR 2.24; 95% CI 1.15 to 4.35; P = 0.017). Both patients with a tunneled cuffed catheter (RR 0.13; 95% CI 0.04 to 0.39; P < 0.001) and patients with an untunneled uncuffed catheter (RR 0.36; 95% CI 0.13 to 1.00; P = 0.05) had lower CRB rates with TSC (Figure 2, Table 2). There were 32 episodes of exit-site infections in the heparin group

Table 2. Summary of the primary and secondary end points.

	Trisodium Citrate Group (N=148) No. of events %	Heparin Group (N=143)	Relative Risk (95% CI)*	P Value
Primary end points				
Catheter-related bacteremia				
All Catheters	9 (6)	33 (23)	0.25 (0.12-0.52)	<0.001
No. per 1,000 catheters days	1.1	4.1		
Tunneled cuffed catheters	4 (8)	19 (40)	0.13 (0.04-0.39)	<0.001
No. per 1,000 catheters days	0.8	4.2		
Untunneled uncuffed catheters	5 (5)	14 (15)	0.36 (0.13-1.00)	0.05
No. per 1,000 catheters days	1.4	3.9		
Removal for any complication				
All Catheters	42 (28)	66 (46)	0.57 (0.38-0.85)	0.005
No. per 1,000 catheters days	5.0	8.1		
Tunneled cuffed catheters	10 (20)	20 (42)	0.38 (0.17-0.83)	0.015
No. per 1,000 catheters days	2.1	4.4		
Untunneled uncuffed catheters	32 (33)	46 (48)	0.69 (0.44-1.08)	0.11
No. per 1,000 catheters days	9.0	12.8		
Secondary end points				
Exit-site infection				
All Catheters	11 (7)	32 (22)	0.41 (0.20-0.81)	0.012
No. per 1,000 catheters days	1.3	3.9		
Tunneled cuffed catheters	5 (10)	13 (27)	0.47 (0.17-1.34)	0.16
No. per 1,000 catheters days	1.0	2.9		
Untunneled uncuffed catheters	6 (6)	19 (20)	0.25 (0.08-0.73)	0.012
No. per 1,000 catheters days	1.7	5.3		
Removal for flow problems				
All Catheters	27 (18)	29 (20)	0.92 (0.54-1.55)	0.75
No. per 1,000 catheters days	3.2	3.6		
Tunneled cuffed catheters	4 (8)	3 (6)	1.23 (0.27-5.48)	0.79
No. per 1,000 catheters days	0.8	0.7		
Untunneled uncuffed catheters	23 (24)	26 (27)	0.87 (0.49-1.54)	0.64
No. per 1,000 catheters days	6.4	7.2		
Catheters treated with urokinase				
All catheters	69 (47)	63 (44)	1.11 (0.70-1.75)	0.72
Tunneled cuffed catheters	20 (40)	22 (46)	0.79 (0.35-1.76)	0.56
Untunneled uncuffed catheters	49 (50)	41 (43)	1.32 (0.75-2.32)	0.34
Admissions for CR-infection (no.)	6	21	0.25 (0.09-0.63)	0.002
No. per 1,000 catheters days	0.7	2.7		
Death from any cause	13	18	0.67 (0.31-1.43)	0.20
Death from catheter-related bacteremia	0	5	0.96 (0.93-0.99)	0.028

The effect of the treatment assignment on catheter survival and bacteremia was determined with stratification according to clinical center and type of catheter and was adjusted for the following prespecified baseline factors: Age, gender, race, years of dialysis, presence or absence of diabetes, malignancy, cardiovascular disease, acute renal failure, hospitalization, use of coumarin, and nasal carriage of Staphylococcus aureus. TSC, trisodium citrate; RR, relative risk; CI, confidence interval; CRB, catheter-related bacteremia.

versus 11 in the TSC group (P = 0.012). In seven of 42 periods of CRB, a concurrent exit-site infection was apparent, equally divided between the treatment groups. All-cause mortality did not differ significantly, but the number of deaths from CRB was lower in the patients with TSC-locked catheters compared with heparin (0 versus 5 patients; RR 0.96; 95% CI 0.93 to 0.99; P = 0.028). Also, the number of admissions for CRB decreased from 21 to six (P = 0.002).

Table 3. Adverse and Bleeding events.

Locking procedures	Trisodium Citrate Group N=6208	Heparin Group N=6416	P Value
Adverse event	no. of events		
Parasthesia, "metallic taste", tingling in fingers immediately after locking	9	4	0.26
Thrombopenia of unknown origin	2	4	0.44
Withdrawal for medical reasons (persistent bleeding disorder)	0	1	0.49
Bleeding events			
Persistent bleeding after insertion	6	19	0.005
Severe	0	2	0.24
Major bleeding episodes during follow up			
Total	5	16	0.010
No. per 1,000 catheters days	0.60	2.0	
Gastrointestinal bleeding	1	7	0.034
Exit-site bleeding	0	5	0.028
Hemorrhagic ascites after peritoneal dialysis catheter removal	1	1	0.74
Hematuria	0	1	0.49
Postoperative bleeding	2	2	0.68
Hemoptoe in pulmonary malignancy	1	0	0.51

In 71% of CRB cases, cultures yielded Gram-positive microorganisms, predominantly S. aureus or S. epidermidis; in 10%, it concerned Gram-negative microorganisms. The remaining cultures revealed multiple microorganisms. No yeasts were found. Cultures in exit-site infections revealed similar results.

Thrombotic Complications

Twenty-nine of the 143 catheters assigned to heparin locking had to be removed because of persistent flow problems (3.6 per 1000 catheter-days), and 27 of 148 catheters assigned to TSC had to be removed (3.2 per 1000 catheter-days; RR 0.92; 95% CI 0.54 to 1.55; *P* = 0.75). The need for locally installed urokinase or systemic urokinase administration was not significantly different in the treatment groups (Table 2). During the period that the catheter was in place, 80 of 143 catheters assigned to heparin did not need thrombolytic treatment of any kind (56%), and 79 of 143 assigned to TSC did not need thrombolytic treatment (53%; Table 2). Having an untunneled catheter was the only independent risk factor for premature removal

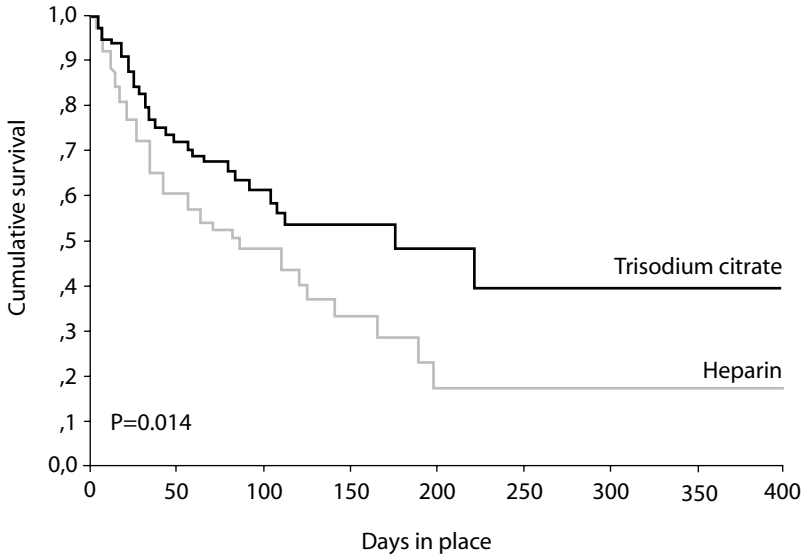

Figure 1. Kaplan-Meier analysis of catheter survival for the locking solutions. The *P* value was calculated with use of the log-rank test.

because of flow problems (adjusted RR 6.82; 95% CI 3.05 to 15.25; P < 0.001). Excluding patients with a femoral catheter provided similar results for tunneled and untunneled catheters.

Safety, Adverse Events, and Bleeding Episodes

A total number of 12,624 locking procedures were registered (Table 3). No serious adverse events that could be contributed to the locking solution were reported in both groups. Eighteen patients in the heparin group and 13 patients in the TSC group died while having a catheter in place (*P* = 0.20; Table 2). Nine patients immediately after locking with TSC and four patients after heparin locking reported symptoms, mostly perioral

or peripheral paresthesia or a "metallic" taste. Symptoms disappeared within 1 min of instillation and did not return in all patients after reduction of the volume used for locking. Unexplained thrombocytopenia was found in four patients on heparin and two on TSC. One patient in the heparin group was withdrawn from the study because of persistent prolonged coagulation times and bleeding complications.
Persistent bleeding from the place of insertion immediately after catheter placement was reported in 19 patients in the heparin group compared with six in the TSC group ($P = 0.005$). During follow-up, 16 patients in the heparin group experienced a major bleeding episode compared with five patients in the TSC group ($P = 0.01$).

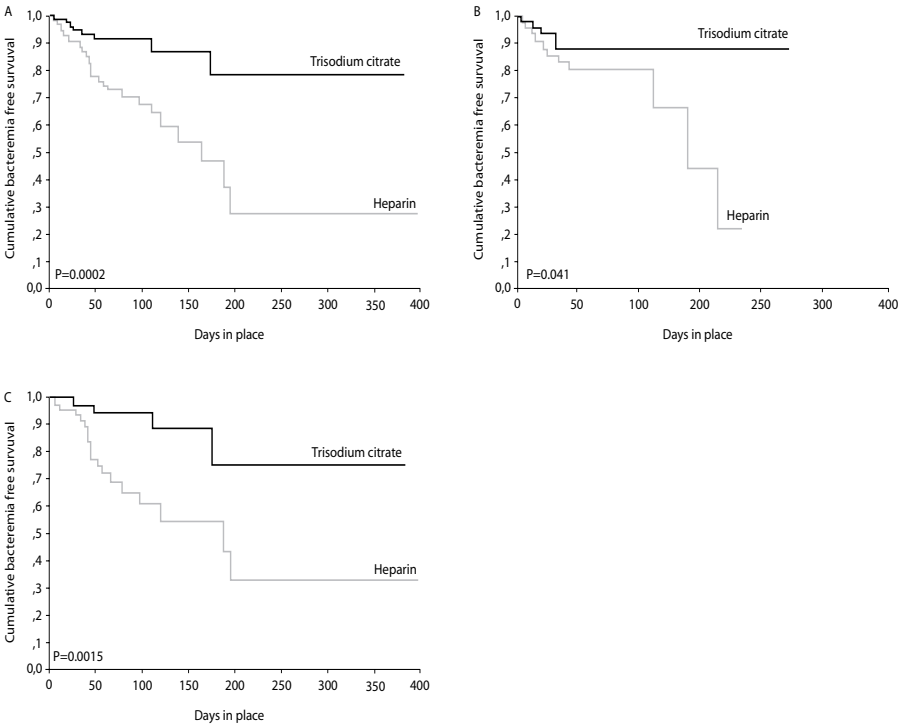

Figure 2. *Kaplan-Meier analysis of the probability that patients would remain free of catheter-related bacteremia for all catheters (A) and for the subgroup with untunneled uncuffed catheters (B) and the subgroup with tunneled cuffed catheters (C). The P values were calculated with the use of the log-rank test.*

DISCUSSION

The results of this study show that for hemodialysis catheters, an interdialytic lock of TSC 30% is more effective in preventing premature removal than heparin.
TSC reduced the risk for CRB by 75% and reduced the number of patients who died from this serious complication of hemodialysis catheter use. The findings were consistent among the subgroups of patients with tunneled and untunneled catheters.
Our results are in agreement with a previous observational catheter-lock study that used high concentrations of TSC. Ash *et al*. (24) observed an average decline in bacteremia of 4.5 to 0% per month in all patients after switching from heparin to high concentration TSC for hemodialysis catheter locking. So far, only a few open-label comparative studies showing no clear differences between TSC and heparin have been published (25,30). These studies, however, accounted for only approximately 5,000 catheter-days of pooled data and mostly used lower concentrations of TSC. Adding antibiotics to a locking solution can also prevent CRB. However, widespread use cannot be recommended because the addition of antibiotics in solutions for interdialytic locking of catheters can cause severe side effects through leakage from the tip, resulting in continuous systemic levels of the antibiotic, especially aminoglycosides (19,20).
Taurolidine-containing solutions have shown promising results. Their limited availability and high costs, however, preclude their use in clinical practice so far (31).
Our study results are likely to be valid because of the random assignment to treatment groups and the use of a double-blind design. In addition, our study included an average hemodialysis population with catheter-related complications similar to that reported in previous studies (5–7,9,32). Furthermore, we stratified patients for center and type of catheter to rule out the influence of local differences in catheter care.
All patients with suspected bacteremia had at least two sets of blood cultures drawn from their catheter. Peripheral blood cultures through separate venipuncture sites were not routinely performed. However, it is unlikely that we overestimated the amount of CRB because in our definition we considered a CRB only apparent if the patient had cold chills with positive blood cultures and no other obvious cause of infection. This definition is also used in most other catheter studies because it precludes the need for more punctures for the patients and increases the chance to consent to the study protocol (6,7,9,33).
We could not show a reduction in premature removals because of thrombotic complications; neither was the use of urokinase for catheter flow problems reduced, suggesting that the mechanism of flow problems is not related to intraluminal biofilm formation. Probably, catheter tip construction and fibrin sheath formation on the outside of the catheter are more important in the pathogenesis of flow problems (8,34,35).
Concerning reduction of patency rates, we could show only a trend and no significant difference in untunneled catheters. This is probably explained by the limited number of untunneled catheter-days included in this study and that many more untunneled catheters had to be removed prematurely because of flow problems. This study is the first that clearly demonstrates that locking of a catheter with heparin is an important cause of bleeding complications in hemodialysis patients. This is in agreement with the occasional observations reported in other studies (16,18). The probable explanation is that locking catheters with heparin leads to unintentional leakage of heparin from the

catheter, resulting in prolonged bleeding times. This makes patients vulnerable to bleeding complications.
We demonstrated that TSC 30% can be used safely as catheter-lock solution. Side effects with TSC have been reported only immediately after locking and are not the result of persistent leakage from the tip during the period when the catheter is locked.
The symptoms are probably caused by a temporary drop in Ca^{2+} and Mg^{2+}. They disappear after 30 to 60 s because of the large buffer of Ca^{2+} and Mg^{2+} in whole blood. There is no solid theoretical base to suggest that prolonged use or multiple locking solutions needed in permanent tunneled cuffed catheters will increase the risk more than individual locking procedures. A total of 12,624 locking procedures were registered.
No serious adverse events that could be contributed to the locking solution were reported in both groups. Recently, Stas *et al*. (25) confirmed this finding in a study that compared heparin 5,000 IU/ml and TSC 30% for the evaluation of catheter thrombus formation. It is clear that these potent solutions should be used only by authorized and skilled personnel and that the introduction must be accompanied by a thorough protocol (36). At present, in the majority of Dutch dialysis units, TSC is used for catheter locking with a strict protocol, and no serious adverse events have been reported.
We did not include a cost-effectiveness analysis in this study as TSC is relatively inexpensive. Prepared from raw base, it is approximately 10-fold less expensive than heparin. However, as was already discussed in the introduction, the reduction of expenditures for vascular access will be impressive when catheter-related complications can be prevented.
In conclusion, the use of TSC 30% for catheter locking in hemodialysis can contribute importantly to the reduction of catheter-related complications in hemodialysis patients by prevention of premature catheter removal and catheter-related infections. Probably, even a reduction in bacteremia-related death can be achieved.
In addition, bleeding complications from unintentional heparinization can be reduced.

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7 Summary and future directions

7

TEMPORARY VASCULAR ACCESS FOR HEMODIALYSIS TREATMENT.

For patients requiring hemodialysis treatment a reliable access to the blood stream is essential. Vascular access related complications are one of the most important causes of patient morbidity. The National Kidney Foundation – Dialysis Outcomes Quality (NKF-DOQI) Initiative committee recommends the use of a forearm arteriovenous (AV) fistula because these have demonstrated the best overall patency and lowest risk for complications. However, in a significant number of patients requiring hemodialysis treatment there is no adequate AV access available because they present with acute renal failure or have slow maturation of their fistula or failure of their permanent arteriovenous access. When hemodialysis treatment can not be postponed, these patients require a temporary vascular access by means of a hemodialysis catheter. Guidelines recommend that no more than 10% of prevalent hemodialysis patients should have a catheter for access. However, in current practice, the use of catheters for hemodialysis treatment is still substantial. Such widespread application of catheters exposes patients to an enhanced risk of catheter-related complications. As a consequence of these complications about 50% of all temporary catheters have to be replaced resulting in substantial patient morbidity as well as additional costs. In order to prevent the most important catheter-related complications, i.e. infection and thrombosis, and to optimize the survival of a catheter, an appropriate estimation of the duration a catheter will be needed is most important. The optimal site of insertion must be chosen, the right type of catheter and whether the catheter should be tunneled or not. In addition, the access team must determine what kind of dressing should be used and whether antimicrobial ointment and/or antimicrobial locking solutions should be applied. Optimalization of catheter care remains an important issue in hemodialysis treatment as the use of catheters will probably only increase in the growing number of patients requiring dialysis treatment. Especially as the age of these patients is increasing and the duration they stay on hemodialysis has become longer.

COMPARISON OF OUTCOME OF TEMPORARY CATHETERS AT DIFFERENT SITES AND OF DIFFERENT CONSTRUCTION

In **Chapter 3** we examined the best cannulation site once the time period that a hemodialysis catheter is needed has been estimated. According to the NKF-DOQI guidelines, the subclavian vein should not be used because of a high risk of subclavian vein thrombosis. Untunneled femoral catheters should not be left in place for more than 5-7 days because of the high risk for infections. For untunneled jugular catheters, the recommendation is not to use these for more than 3-4 weeks and insert a tunneled jugular catheter when a catheter is needed for longer time periods. However, no clinical studies support these time limitations.

In our first study we evaluated the outcome of untunneled straight jugular, femoral and subclavian catheters and tunneled cuffed catheters. To relate our results to the NKF-DOQI guidelines, we focused on the survival and infection rates for the time period of four weeks as especially untunneled jugular catheters could be a reasonable alternative to tunneled cuffed catheters for this period of time. The unique feature of our study is that we used a similar catheter care protocol for all catheters and corrected for differences

in patient characteristics. Compared to previous reports, this results in a more reliable comparison between catheter groups. We could demonstrate that even when a catheter is needed for only 14 days, tunneled cuffed catheters had the best survival and lowest infection rates. Femoral catheters had a high risk of complications when they were left in place for more than 7 days. We also showed that the risk for an adverse outcome increased linearly over time. These findings implicate that almost all catheters for hemodialysis treatment should be tunneled. However, earlier use of tunneled cuffed catheters must be weighted against the more time consuming and difficult insertion and removal of tunneled cuffed catheters and the higher costs. This is probably the reason that in current practice untunneled catheters are still widely used and left in place longer than guidelines recommend.

We hypothesized that one of the major reasons of the low patency rates of untunneled straight jugular catheters was the difficulty to fixate these catheters adequate. This leads to more manipulation and can easily give laceration and secondary infection of the exit-site, well known risk factors for subsequent catheter-related bacteraemia. In addition, straight jugular catheters have an upward directed exit site, a well established risk factor for exit-site infections and subsequent systemic infection because adequate drainage of debris is prohibited.

In **Chapter 4** we describe the effect of the use of a novel precurved untunneled jugular catheter on catheter-related complications. The precurved untunneled catheter used in this study has improved fixation properties and the advantage of a forward to downwardly directed exit-site that makes adequate drainage of debris possible. We also addressed the time recommendations found in the previous study, including the question when a tunneled cuffed hemodialysis catheter should be used.

Our study demonstrated that this novel forwardly bended precurved haemodialysis catheter inserted in the low jugular site had a better survival and lower risk for infection compared to a straight jugular catheter. Infection rates for the novel designed catheter did not differ from the rates found in tunneled cuffed catheters. Considering catheter-related infections as major drawback for catheter use, our results demonstrated that an untunneled precurved catheter for the period of three months could be a safe option. Furthermore, it was more convenient for the patient, easier for the physician during insertion and probably cost-saving. However, compared to tunneled cuffed catheters, more untunneled precurved catheters had to be removed for flow problems. This is possibly caused by the fact that untunneled cuffed catheters have a smaller diameter. Most likely, the function of untunneled precurved catheters can be improved by increasing its diameter and tip construction.

CLINICAL IMPLICATIONS OF HEMODIALYSIS CATHETER CONSTRUCTION

Catheters basically serve a simple purpose: "to guide the venous blood towards the dialysis machine and bring it into the venous system again in a safe and reliable way". Therefore, it is remarkable that the geometry and tip design of catheters differ substantially and have been determined mainly by methods of trial and error.

The common believe is that multiple side holes are needed to provide backup in case the distal or some of the side holes get obstructed by venous wall suction or a fibrin sleeve.

However, side holes can also hamper catheter fluid dynamics and induce thrombosis.
In **Chapter 5** we evaluated the performance of four different types of tunneled and untunneled dual lumen catheters in an in vitro set-up by studying their pressure-flow relationship. The calculated equivalent catheter diameter is a parameter that allows comparing the pressure-flow data of different catheters independently from the test fluid used and the length of the catheter. The calculated equivalent catheter diameter is derived from the pressure-flow relationship of catheters. This is especially useful for dual lumen catheters as for some designs (co-axial, double D-shaped) there exists no clear definition for the diameters of the individual limbs, which makes it harder to compare their geometrical data with independent full round single lumen catheters.
From the measurements and calculations we could show that the construction of tunneled catheters is superior to the construction of acute catheters. We also showed that double-D catheters perform better than catheters with a coaxial internal lumen.
We have also investigated the influence of closing off some of the side-holes to see how that would impact catheter performance. It was concluded that multiple side holes generally and under the ideal circumstances of the presented in vitro set-up did not improve catheter performance. This is probably caused by the occurrence of local velocity changes both in direction as in magnitude during inflow to or outflow from side holes. Local velocity changes can also be caused by the tapered shape of catheter tips.
We demonstrated that the recommended blood flow for effective hemodialysis treatment delivery, i.e.
300 ml/min, can only be achieved in the acute catheters with pressure drops of over 300 mmHg. These pressures can not easily be attained in modern dialysis equipment and can easily cause blood lysis through high shear stress. So far, only a limited number of small clinical studies have been published comparing different types of catheters and no clinical advantage has been shown of one model over an other. Therefore, more clinical studies are needed to estimate the implications of our findings for hemodialysis practice.
It is also not clear whether silicone or polymers like polyurethane should be the preferred material for hemodialysis catheters. Catheter fractures in small non-hemodialysis catheters have been reported, especially with silicone catheters. The reason for these fractures is unknown and it is not clear whether catheter material is relevant.
In the second part of **Chapter 5** we describe the first case of an asymptomatic spontaneous breakdown of a tunneled cuffed silicone catheter used for long-term hemodialysis treatment. An extensive scanning electron microscopy study showed accumulation of lumps of non-silicone material at the place of the fracture, leading to severe disruption of the original cross-linked elastomer structure.
Using energy-dispersive X-ray spectral analysis, which shows all elements with an atomic number of 11 or greater in a material, we showed that the lumps were aggregates of barium sulphate particles used to visualize the catheter on fluoroscopy. We suggested that the use of too small or too many barium sulphate particles led to high viscosity of the raw silicone before polymerization, causing improper mixing of barium sulphate particles in the silicone matrix. This resulted in insufficient removal of admixed air bubbles and unequal dispersion of barium sulphate, causing weak spots after extrusion of

the silicone into its definitive shape.
As polyurethane polymers are easier to process, have higher traction resistance and have less restriction which cleansing solutions. We assume that in the future, silicone will most likely be replaced as material for hemodialysis catheter manufacturing by these polymers.

LOCKING SOLUTIONS

The internal lumen of hemodialysis catheters has to be filled (locked) with a solution for the interdialytic period. Traditionally, heparin is installed but there are no studies to support this practice. Locally acting antimicrobial locking solutions could be an attractive alternative as they can prevent microbial catheter colonization, a well known risk factor for catheter-related bacteraemia. Furthermore, it is well known that locking solutions leak from the tip of the catheter. Through this phenomenon, heparin might be causing clinical problems because of unintentional systemic anticoagulation. Whether this feature has clinical implications is not clear. Trisodium citrate (TSC) has been proposed as locking solution because it is a locally acting anticoagulant, might have antimicrobial properties in high concentrations and is widely available and inexpensive.
We hypothesized that a high concentration of TSC as locking solution could reduce catheter-related infections and bleeding complications. However, the optimal concentration of TSC remained to be determined. In **Chapter 6** we describe the studies that evaluated the optimal concentration of TSC and the results of a large clinical trial using TSC as locking solution. In the first study we analysed the antimicrobial properties of 4 different concentrations of TSC against five different microorganisms frequently encountered in catheter-related infections in hemodialysis patients. As no standardized methods are available for testing antimicrobial activity of catheter locking solutions, we used two internationally standardized classical antimicrobial susceptibility tests modified for fluids. We demonstrated that the antimicrobial activity was dose dependent with the highest efficacy for TSC 30%. Although previously suggested by others, we also could show that the explanation for the antimicrobial properties of higher concentrations of TSC does not seem to be the hyperosmolality as in both tests the antimicrobial activity of TSC exceeded that of isoosmolal NaCl concentrations. We suggested that it is more likely that chelating effects of Ca^{2+} and Mg^{2+} by TSC interfere with bacterial wall integrity and prevent biofilm formation. We concluded from this study that the use of high concentrations of TSC for catheter locking could have an advantage over heparin but should be evaluated in a multicenter double blind randomised controlled trial before introduction into clinical practice.
Results of this trial are described in the second part of **Chapter 6**.
In one of the largest randomized studies on hemodialysis catheters we demonstrated that trisodium citrate 30% is more effective in preventing premature removal than heparin. TSC reduced the risk for catheter-related bacteraemia by 73%, the main reason that the study was terminated prematurely. Locking hemodialysis catheters with TSC even reduced the number of patients that died from catheter-related bacteraemia.
The findings were consistent among subgroups of patients with tunneled and untunneled catheters. We could not show a reduction in premature removals because of thrombotic complications. Neither was the use of urokinase for catheter flow problems

reduced. This suggests that the mechanism of flow problems is not related to intra-luminal biofilm formation. More likely, catheter tip construction and fibrin sheath formation on the outside of the catheter are more important in the pathogenesis of flow problems.
This study is the first that clearly demonstrated that locking of a catheter with heparin is an important cause of clinically important bleeding complications in hemodialysis patients. The probable explanation is that locking catheters with heparin leads to unintentional leakage of heparin from the catheter, resulting in prolonged clotting times. We demonstrated that TSC 30% can be used safely as catheter lock solution as a total number of 12,624 locking procedures were registered without serious adverse events.
We concluded that the use of TSC 30% can contribute importantly to the reduction of catheter-related complications in hemodialysis patients and should replace heparin as catheter lock solution in hemodialysis catheters.

FUTURE DIRECTIONS

Dedicated vascular access teams for hemodialysis patients will reduce the number of catheters by initiation of early construction of an arteriovenous fistula. According to the NKF-DOQI guidelines, patients with deteriorating renal function should be referred to and cared for by a nephrologist when their GFR has become lower than 30 ml/min. When the GFR has become lower than 20-25 ml/min, an evaluation of venous and arterial vessels of both arms should be performed to assess and decide which AV-access is feasible. If possible, a forearm AV-fistula should be constructed.
However, despite maximum efforts to reduce the use of hemodialysis catheters for access to the blood stream, patients with acute renal failure, sudden renal graft failure, irreversible peritonitis during peritoneal dialysis requiring peritoneal catheter removal, acute failure of their chronic AV-access or simply late referral of patients with chronic renal failure are all reasons for persistent need for catheters in the future. Most likely, its use will not become less than 5-10% of all vascular access in a general hemodialysis ward. However, it is very likely that the number of hemodialysis catheter-related complications will decrease drastically because of the recent progress that has been made in catheter care and manufacturing. Currently, by implementing strict aseptical protocols, antimicrobial ointments for exit-site care and antimicrobial solutions for catheter locking, the risk for the most serious catheter-related complication, i.e. bacteraemia, has become less than 1 per 1000 catheter days. Currently, this is at a level of infection rates found in patients with AV-grafts.
Promising progress is made with coating of catheters. In intensive care patients, catheters coated with antibiotics, silver or heparin reduce the number of infections substantially. A problem with bonding in hemodialysis catheters is that they are often needed for a longer period of time and the substance impregnated or bonded on catheters can disappear over time. However, new materials that improve biocompatibility, like carbothene, are already used and the risk for fibrin sheet formation and catheter related thrombosis will likely reduce.

Currently, large bore precurved hemodialysis catheters for insertion in the jugular vein have become available and are under evaluation. Because flow-pressure curves of these catheters are at least comparable to tunneled cuffed catheters, catheter related thrombosis and flow problems will probably be reduced to an acceptable level.
It is necessary that these new catheters, that require less skills and time from the inserting physician are tested in a randomized controlled trial because they can mean an important improvement in catheter care. From current experiences and evaluations, it can be expected that the results will show that untunneled precurved jugular catheters will be a safe alternative to tunneled cuffed catheters for the period of 3-4 months.
This is the period that is normally needed in most patients to construct a definitive AV-access. In the growing number of very old patients becoming dependent on hemodialysis treatment, construction of an AV-access is often difficult and leads to substantial morbidity and hospitalization. As catheter-related complications will be reduced
by recent developments, it may even be warranted to evaluate if a hemodialysis catheter could be an attractive alternative as definitive access in these patients as they have a limited life expectancy.
After introduction into clinical use, hemodialysis catheter practice has mainly been guided by trial and error and guidelines were based on personal opinions. In the past decade hemodialysis catheter-related complications have been reduced drastically by performing thorough multicenter clinical trials. This progress can only be continued with the help of enthusiastic teams of nephrologists and nurses, supported or even guided by scientists and academical departments, willing to collaborate in studies.

8 Samenvatting

Strategieën om het aantal complicaties bij hemodialyse katheters te reduceren

INLEIDING

Patiënten met eindstadium nierfalen zijn aangewezen op nierfunctievervangende therapie. Omdat niertransplantatie niet voor iedereen (direct) mogelijk is, zijn veel patiënten tijdelijk of voorgoed aangewezen op dialysebehandeling. De meest gekozen behandeling is in dat geval hemodialyse. Bij een hemodialysebehandeling wordt gewoonlijk drie maal per week gedurende vier uur bloed van de patiënt naar een dialyseapparaat geleid waar afvalstoffen uit het bloed worden verwijderd. Het gezuiverde bloed wordt daarna teruggeleid naar de patiënt. Hiervoor is een goede toegang tot de bloedbaan noodzakelijk. Een verbinding tussen slagader en ader van eigen bloedvat of eventueel kunststof materiaal (arterioveneuze shunt) heeft hiervoor de voorkeur. Deze verbinding wordt meestal aangelegd op de onderarm en bij elke behandeling met twee naalden aangeprikt. De patiënt moet hiervoor echter geopereerd worden waarna het meestal nog weken duurt voordat deze shunt daadwerkelijk kan worden gebruikt.
Als hemodialyse behandeling echter niet kan worden uitgesteld, is de enige mogelijkheid het inbrengen van een dubbellumen katheter. Deze kan worden ingebracht in een grote ader in de lies (*vena femoralis*), onder het sleutelbeen (*vena subclavia*) of laag in de hals (*vena jugularis*). Katheters zijn vaak maanden nodig en worden niet steeds opnieuw ingebracht. Een katheter in de liesvene is erg onpraktisch voor een patiënt en raakt snel geïnfecteerd. Een katheter in de sleutelbeenvene geeft een verhoogd risico op het verstopt raken van de ader die later misschien nog nodig is voor het aanleggen van een arterioveneuze shunt. Om die redenen gaat de voorkeur uit naar een katheter in de halsvene. Soms worden ze eerst een stuk onderhuids getunneld voordat ze de bloedbaan ingaan, voornamelijk omdat verondersteld wordt dat dit infecties kan voorkomen. Het gebruik van katheters gaat echter gepaard met complicaties, zoals infecties. Hiervan is bacteriële bloedbaaninfectie de meest gevaarlijke en potentieel levensbedreigend. Een ander veel voorkomend probleem is dat katheters verstopt kunnen raken. Deze complicaties leiden ertoe dat de helft van de katheters voortijdig verwijderd en vervangen moeten worden.
De studies beschreven in dit proefschrift hebben tot doel de complicaties gepaard gaande met het gebruik van hemodialysekatheters te verminderen.

VERGELIJKING VAN VERSCHILLENDE SOORTEN KATHETERS INGEBRACHT OP VERSCHILLENDE PLAATSEN

In **hoofdstuk 3** beschrijven we de resultaten van een studie waarin de complicaties die gepaard gaan met het gebruik van ongetunnelde katheters ingebracht in de liesvene, sleutelbeenvene en halsvene met elkaar worden vergeleken en met getunnelde katheters. We konden aantonen dat ongetunnelde katheters in de lies al binnen een week meer complicaties geven dan getunnelde katheters. Voor ongetunnelde katheters ingebracht in de halsvene betroffen de complicaties vooral infecties. Al na twee weken was de kans op complicaties en infecties hoger bij het gebruik van ongetunnelde katheters ten opzichte van getunnelde. Volgens de bevindingen van dit onderzoek zou dus moeten worden gekozen voor een getunnelde hemodialyse katheter wanneer mag

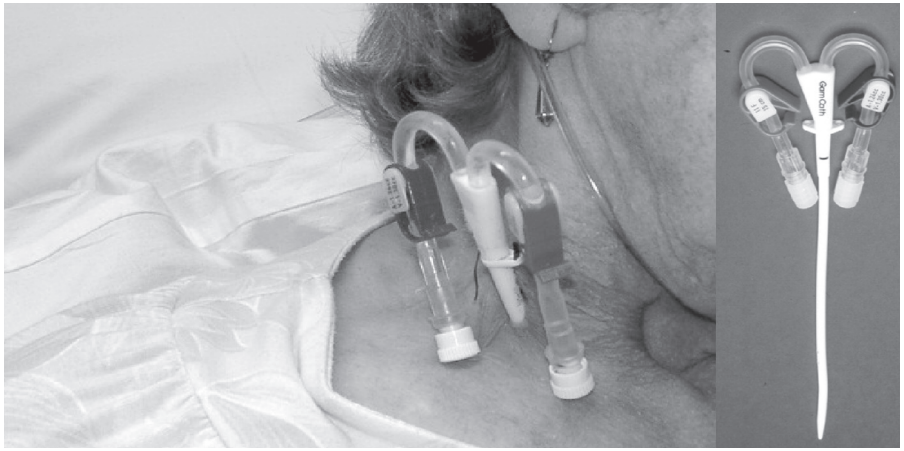

Foto 1. Rechte katheter in de halsvene met omhoog gerichte huidpoort.

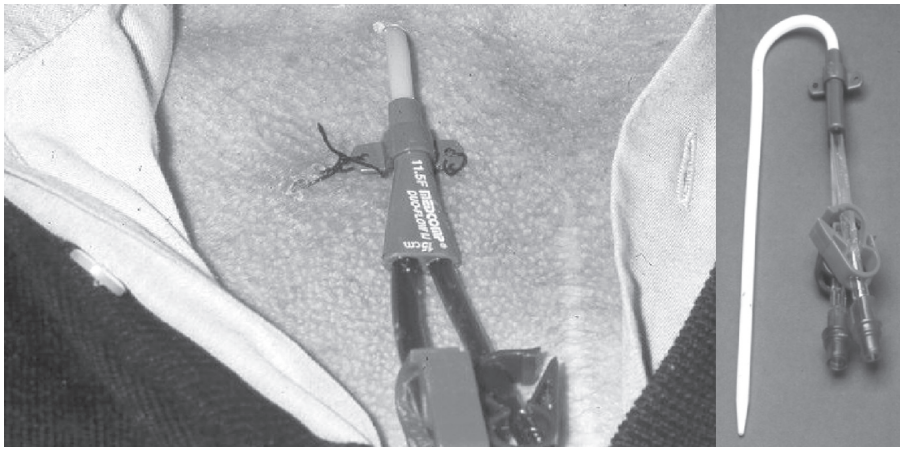

Foto 2. Voorgebogen katheter met naar beneden gerichte huidpoort.

worden verwacht dat een katheter meer dan twee weken nodig is. Dit is voor de meeste katheters het geval. In tegenstelling tot het inbrengen van ongetunnelde katheters is echter het inbrengen en later verwijderen of vervangen van getunnelde katheters een lastige procedure die relatief veel tijd kost en niet door iedere chirurg of nierspecialist (nefroloog) wordt beheerst. Dit is de reden dat de behandelende arts in de dagelijkse praktijk nog te vaak een ongetunnelde katheter in brengt ondanks de voordelen van getunnelde katheters.
Een van de redenen van het verhoogde risico op infecties bij het gebruik van ongetunnelde jugularis katheters is waarschijnlijk het feit dat deze katheters lastig te fixeren zijn. Hierdoor kunnen eenvoudig ongewenste manipulaties aan de katheter

plaatsvinden met beschadiging van de plaats waar de katheter het lichaam ingaat, de huidpoort. De kans op infecties wordt ook verhoogd doordat door de rechte vorm van de katheter de huidpoort omhoog gericht is waardoor zich vuil kan ophopen rondom de insteekplaats van de katheter (foto 1).
In **hoofdstuk 4** beschrijven we resultaten van een studie naar een nieuw model voorgebogen ongetunnelde jugularis katheter die als voordeel heeft dat de fixatie beter is en de huidpoort naar beneden is gericht (foto 2). We konden aantonen dat deze katheter tot aanmerkelijk minder katheter gerelateerde infecties leidt. Gedurende de eerste drie maanden dat deze katheter in de patiënt blijft, blijkt de kans op een infectie even groot als bij gebruik van een getunnelde katheter. Ten opzichte van getunnelde katheters zijn ongetunnelde katheters relatief dun en heeft het uiteinde (tip) vaak een andere vorm. Dit is waarschijnlijk de reden dat in deze studie ongetunnelde katheters sneller gedeeltelijk of geheel verstopt raakten.

STUDIES NAAR DE INVLOED VAN DE CONSTRUCTIE OP DE FUNCTIE VAN EEN HEMODIALYSE KATHETER

Met als doel de zojuist beschreven verschillen in constructie verder te analyseren beschrijven we in **hoofdstuk 5** een onderzoek waarbij we met behulp van een laboratoriumopstelling de verhouding tussen druk en stroomsnelheid van vier verschillende soorten getunnelde en ongetunnelde katheters hebben bestudeerd. We konden concluderen dat de constructie van getunnelde katheters tot veel betere prestaties leidt dan de constructie van ongetunnelde katheters. De combinatie van de relatief dunne diameter en taps toelopende tipconstructie van de onderzochte ongetunnelde katheters leidt ertoe dat zeer hoge drukken nodig zijn om voldoende stroomsnelheid voor effectieve dialysebehandeling te genereren. Vaak is dit hoger dan een normaal hemodialyse apparaat kan leveren. Ook vonden we dat zijgaten, hoewel in vrijwel alle katheters aangebracht door de fabrikanten, vanuit het perspectief van doorgankelijkheid en stroomsnelheid ongewenst zijn. In het eerste deel van **hoofdstuk 5** beschrijven we een uitgebreide speurtocht naar de oorzaak van een spontaan in een patiënt afgebroken hemodialysekatheter. Hieruit wordt duidelijk dat het verwerken van siliconen tot een dialyse katheter een delicaat proces is.

OPVULVLOEISTOFFEN

Tussen de hemodialysebehandelingen wordt in het lumen van een katheter een vloeistof achtergelaten om verstopping van de katheter te voorkomen. Tot voor kort werd hiervoor het antistollingsmiddel heparine gebruikt. Lekkage van dit middel uit de tip van de katheter zou echter mogelijk bloedingen kunnen veroorzaken als gevolg van ongewenste systemische antistolling van een patiënt. Mogelijk hebben antistollingsmiddelen die alleen lokaal werken dat nadeel niet. Van enkele van deze oplossingen wordt gesuggereerd dat ze ook een antimicrobiële werking hebben. Dit zou katheter gerelateerde infecties kunnen voorkomen. Ons onderzoek heeft zich gericht op trinatrium citraat (TNC) oplossingen omdat deze al voor andere medische toepassingen beschikbaar waren en goedkoop zijn. In het eerste deel van **hoofdstuk 6** hebben we met behulp van een laboratoriumstudie de antimicrobiële

werking van verschillende concentraties TNC geanalyseerd. We vonden dat hoge concentraties nodig zijn voor optimale antimicrobiële werking. Ook konden we aantonen dat heparine geen antimicrobiële werking heeft. Het mechanisme waardoor TNC antimicrobiële werking heeft, bleek niet te berusten op de hoge osmolaliteit (deeltjesdichtheid) zoals tot nog toe werd verondersteld. Waarschijnlijk is het wegvangen van calcium en magnesium verantwoordelijk voor de antimicrobiële werking van TNC.
In het tweede deel van **hoofdstuk 6** beschrijven we de resultaten van een gerandomiseerde klinische studie in meerdere ziekenhuizen in Nederland en België waarin TNC 30% werd vergeleken met heparine als opvulvloeistof. In totaal 291 patiënten met katheters werden hiervoor onderzocht. We konden aantonen dat katheters langer gebruikt konden worden als TNC 30% als opvulvloeistof werd gebruikt. Het aantal bloedbaan infecties werd met 73% gereduceerd en er bleken zelfs minder patiënten aan deze gevreesde complicatie te zijn overleden als TNC als opvulvloeistof werd gebruikt. Tevens bleek dat er belangrijk minder bloedingen, zoals maagdarmbloedingen, optraden bij patiënten bij wie TNC 30% als opvulvloeistof was gebruikt. De resultaten van deze studie hebben ertoe geleid dat in meer dan 80% van de hemodialysecentra in Nederland heparine vervangen is door TNC.

CONCLUSIE

Dit proefschrift beschrijft de belangrijkste problemen waar patiënten, dialyseverpleegkundigen en nefrologen ondervinden als een katheter noodzakelijk is om toegang tot de bloedbaan te krijgen voor hemodialyse behandeling. Katheters zullen voorlopig noodzakelijk blijven. Het is daarom belangrijk dat door zorgvuldig uitgevoerd wetenschappelijk onderzoek wordt gekeken hoe complicaties kunnen worden gereduceerd. Wij hebben geprobeerd hieraan een bijdrage te leveren. In de afgelopen jaren is door dit soort onderzoek en de toegenomen aandacht voor katheter gerelateerde problemen de zorg dusdanig verbeterd dat het aantal infecties in veel hemodialysecentra drastisch verminderd is.
Nieuwe veelbelovende ontwikkelingen dienen zich al weer aan. Ook voor deze ontwikkelingen geldt dat zorgvuldig gekeken moet worden of ze daadwerkelijk een verbetering betekenen voor de zorg aan de hemodialyse patiënt. Daartoe zijn meer wetenschappelijke studies nodig die gezamenlijke inspanning vragen van patiënten, dialyseverpleegkundigen, nefrologen en wetenschappers van universitaire afdelingen en hemodialysecentra. Alleen dan zal de kwaliteit van de zorg voor deze kwetsbare groep patiënten kunnen groeien.

DANKWOORD

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CURRICULUM VITAE

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Marcel Weijmer werd op 7 april 1965 geboren in Kampen. Hij voltooide in 1983 het atheneum aan het Almere College te Kampen. In datzelfde jaar begon hij de studie Geneeskunde aan de Vrije Universiteit te Amsterdam en haalde hij in 1987 het doctoraal examen geneeskunde en in 1990 het artsexamen. Na al in 1986 een onderzoek te hebben gedaan naar hyperthyreoidie in het Sophia ziekenhuis te Zwolle werd in datzelfde ziekenhuis in 1990 verdere ervaring opgedaan in de interne geneeskunde. Hij is daar een jaar als AGNIO werkzaam geweest (opleider dr. T. Tjabbes). In 1991 startte hij de opleiding tot internist in het Sint Lucas Ziekenhuis (toen nog zonder Andreas) (opleider dr. H.B. Schreuder). Vanaf 1994 tot 1997 werd de opleiding voortgezet en afgerond in het VU medisch centrum (opleider prof.dr. J. van der Meer).
Van 1996 tot 1997 was hij daar een jaar werkzaam op de afdeling Intensive Care waar hij onder andere het theoretisch examen van de GIC behaalde. Vanaf 1997 tot 2002 is hij werkzaam geweest als chef de clinique interne geneeskunde en later nierziekten in het VU medisch centrum te Amsterdam. Van 1997-1998 werd hij tevens opgeleid tot nefroloog (opleider prof.dr. A.J.M. Donker). In die tijd werd tevens gestart met promotieonderzoek. Aanvankelijk verrichtte hij onderzoek naar bacteriële overgroei van de dunne darm bij peritoneaal dialyse patiënten en naar biocompatibiliteit van peritoneaal dialyse vloeistoffen. Zijn hart lag echter bij meer klinisch gericht onderzoek en vanaf 1999 werd het onderzoek opgezet naar hemodialyse katheters onder leiding van prof.dr. P.M. ter Wee. Met dit onderzoek werden enkele nationale en internationale prijzen gewonnen. Vanaf 2002 is hij werkzaam in het Sint Lucas Andreas Ziekenhuis als internist-nefroloog. Hij is vader van Bram, Zimme en Jolieke.

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